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THE CLINICAL SIGNIFICANCE OF ABNORMALITIES IN URINE VOLUMES *

T. ADDIS, M.D.

SAN FRANCISCO

The words oliguria, polyuria and nycturia are used in this paper to indicate different types of abnormality in urine volume, although in most dictionaries they have a double meaning and may designate changes either in the frequency of urination or in the amount of urine.

At present these words can be used only in a general descriptive sense, and are only applicable with any certainty in those instances in which the deviation from the volumes ordinarily observed is extreme. This is so not on account of any lack of measurements of the volume of urine in normal persons but because these measurements have been made under such varying conditions that the range of normal variation is wide and its limits uncertain. A definition of oliguria, polyuria and nycturia which would give the terms a quantitative significance requires a statistical determination of the distribution of the urine volumes of normal subjects under carefully selected and controlled conditions.

The conditions most likely to lead to the sharpest differentiation between the volumes from normal persons and those obtained from patients with Bright's disease may be expected to be of such a nature that they impose a strain either on the water excreting capacity of the kidney or on its concentrating capacity. For when a large amount of water is given to a patient whose effective renal tissue has been extremely reduced by disease the volume of urine excreted is much less than normal, while it is greater than normal when no fluids have been taken. Under one set of conditions the volume is too large and under the other set of conditions too small. In either case the volume of urine eliminated by a badly damaged kidney differs widely from the normal, and both conditions are, therefore, suitable for a statistical definition of oliguria, polyuria and nycturia.

I. OLIGURIA; POLYURIA

A. CONDITIONS

Constant Low Water Intake; Urea Administration, Twenty-Four Hour Collections.—In 1916, Addis and Watanabe [1] gave the volumes of

* From the Department of Medicine of Stanford University Medical School.

1. Addis and Watanabe: J. Biol. Chem. **27**:267, 1916.

urine observed in twenty normal adults who were on a constant diet with a total water content of 1,710 c.c. This diet was maintained for six days, and at the commencement of each of the last three twenty-four hour periods 20 gm. of urea, dissolved in 360 c.c. of water, were taken. Since then, additional observations have been made on normal adults so that we now have measurements on twenty-eight persons. In order to decrease the variability, the twenty-four hour volumes of the fourth, fifth and sixth days have been averaged. The mean of these averages is 1,345 c.c.; the standard deviation is ± 178 c.c. and the variability is 13.2 per cent. Table 1 gives the odds against any

TABLE 1.—DEFINITION OF OLIGURIA AND POLYURIA

Conditions: Constant low water intake, urea administration, twenty-four hour collections.

Definition	Volume, C.c.	Odds
Oliguria	775 or less	One normal in 1,450
	799 or less	One normal in 1,030
	811 or less	One normal in 741
	829 or less	One normal in 527
Doubtful	847 or less	One normal in 385
	864 or less	One normal in 286
	882 or less	One normal in 213
	900 or less	One normal in 162
	918 or less	One normal in 122
	936 or less	One normal in 93
	953 or less	One normal in 72
	971 or less	One normal in 56
Normal	1,345 or less	One normal in 2
Doubtful	1,719 or more	One normal in 56
	1,737 or more	One normal in 72
	1,754 or more	One normal in 93
	1,772 or more	One normal in 122
	1,790 or more	One normal in 160
	1,808 or more	One normal in 213
	1,825 or more	One normal in 286
	1,843 or more	One normal in 385
Polyuria	1,861 or more	One normal in 527
	1,879 or more	One normal in 741
	1,897 or more	One normal in 1,030
	1,915 or more	One normal in 1,450

normal person having as great or a greater deviation from the average than those represented by the tabulated volumes. It is, of course, easy to say which volumes are certainly normal and which are as certainly to be classified as oliguria or polyuria. The probability that volumes which fall in the doubtful zones belong to the normal or to the abnormal can be judged from the magnitude of the odds against any normal person giving as great or greater deviations from the average.

B. CONDITIONS

Restriction of Water Intake; Twelve Hour Night Collections.—The subjects were required to abstain from all fluids after breakfast until the next morning when the collection of a twelve hour night urine was completed. Under these conditions, the average volume of urine

was 381 c.c. with a standard deviation of ± 112.5 c.c. and a variability of 29.5 per cent. The odds for given volumes are tabulated in Table 2. These figures are derived from ninety-four measurements on seventy-five normal adults.

C. CONDITIONS

Restriction of Water Intake; Urea Administration; Twelve Hour Night Collection.—The subjects took no fluids of any sort from 6 a. m., except that at 6 a. m. and at 6 p. m.; 20 gm. urea in 200 c.c. of water were taken. Urine was collected from 6 p. m. to 6 a. m. We have thirty measurements on twenty-three normal adults. The average is

TABLE 2.—DEFINITION OF OLIGURIA AND POLYURIA

Conditions: Restriction of water intake, twelve-hour night collection

Definition	Volume of Night Urine, 12 Hours, C.c.	Odds
Oliguria	21 or less	One normal in 1,450
	32 or less	One normal in 1,030
	43 or less	One normal in 741
	55 or less	One normal in 527
Doubtful	66 or less	One normal in 385
	77 or less	One normal in 286
	88 or less	One normal in 213
	100 or less	One normal in 162
	111 or less	One normal in 122
	122 or less	One normal in 93
	133 or less	One normal in 72
	144 or less	One normal in 56
Normal	381 or less	One normal in 2
Doubtful	617 or more	One normal in 56
	628 or more	One normal in 72
	640 or more	One normal in 93
	651 or more	One normal in 122
	662 or more	One normal in 162
	673 or more	One normal in 213
	684 or more	One normal in 286
	695 or more	One normal in 385
Polyuria	707 or more	One normal in 527
	718 or more	One normal in 741
	730 or more	One normal in 1,030
	741 or more	One normal in 1,450

639 c.c.; the standard deviation is ± 153.5 c.c. and the variability is 24.0 per cent. The odds for various volumes are given in Table 3.

D. CONDITIONS

Large Water Intake; Urea Administration; Hourly Collections at Height of Diuresis.—These collections were made under the conditions of the ratio test, which has already been described.[2] The largest of the three hourly volumes was taken. The average of thirty-five measurements on twenty-five normal adults was 643 c.c.; the standard deviation was ± 88 c.c. and the variability was 13.7 per cent. The odds are given in Table 4.

2. Addis: Arch. Int. Med. **30**:378 (Sept.) 1922.

TABLE 3.—Definition of Oliguria and Polyuria

Conditions: Restriction of water intake, administration of urea, twelve-hour night collection.

Definition	Volume, C.c.	Odds
Oliguria	163 or less	One normal in 1,060
	178 or less	One normal in 740
	194 or less	One normal in 527
Doubtful	209 or less	One normal in 385
	225 or less	One normal in 286
	240 or less	One normal in 213
	255 or less	One normal in 162
	271 or esls	One normal in 122
	286 or less	One normal in 93
	301 or less	One normal in 76
	317 or less	One normal in 56
Normal	639 or less	One normal in 2
Doubtful	961 or more	One normal in 56
	977 or more	One normal in 72
	992 or more	One normal in 93
	1,007 or more	One normal in 122
	1,023 or more	One normal in 162
	1,038 or more	One normal in 213
	1,053 or more	One normal in 286
	1,069 or more	One normal in 385
Polyuria	1,084 or more	One normal in 527
	1,100 or more	One normal in 741
	1,115 or more	One normal in 1,030

TABLE 4.—Definition of Oliguria and Polyuria

Conditions: Large water intake, urea administration, hourly collections at height of diuresis.

Definition	Volume, C.c.	Odds
Oliguria	361 or less	One normal in 1,450
	370 or less	One normal in 1,030
	379 or less	One normal in 741
	388 or less	One normal in 527
Doubtful	397 or less	One normal in 385
	405 or less	One normal in 286
	414 or less	One normal in 213
	423 or less	One normal in 162
	432 or less	One normal in 122
	441 or less	One normal in 93
	449 or less	One normal in 72
	458 or less	One normal in 56
Normal	643 or less	One normal in 2
Doubtful	828 or more	One normal in 56
	837 or more	One normal in 72
	845 or more	One normal in 93
	854 or more	One normal in 122
	863 or more	One normal in 162
	871 or more	One normal in 213
	881 or more	One normal in 286
	889 or more	One normal in 385
Polyuria	898 or more	One normal in 527
	907 or more	One normal in 741
	916 or more	One normal in 1,030
	925 or more	One normal in 1,450

II. NYCTURIA

Nycturia signifies an increase in the amount of urine excreted during the night as compared with the day. Although the word has hitherto been used to denote changes in the proportion of the night volume only, there does not seem to be any good reason why it should not be employed to indicate the excretion during the night of an unusually large proportion of the solid constituents of the urine. Definitions of nycturia for urea as well as for urine volume are therefore given.

TABLE 5.—DEFINITION OF NYCTURIA.

Volume of urine during night as percentage of twenty-four hours volume. Conditions: Constant low water intake, urea administration.

Definition	Night Volume as Percentage of 24 Hours' Volume	Odds
No nycturia	33.8 or more	One normal in 2
Doubtful nycturia	44.98 or more	One normal in 56
	45.50 or more	One normal in 72
	46.03 or more	One normal in 93
	46.58 or more	One normal in 122
	47.10 or more	One normal in 162
	47.62 or more	One normal in 213
	48.17 or more	One normal in 286
	48.70 or more	One normal in 385
Nycturia	49.22 or more	One normal in 527
	49.75 or more	One normal in 741
	50.30 or more	One normal in 1,030

TABLE 6.—DEFINITION OF NYCTURIA

Urea in night as percentage of urea in twenty-four hours. Conditions: Constant low water intake, urea administration.

Definition	Night Urea as Percentage of 24 Hours' Urea	Odds
No nycturia	33.4 or more	One normal in 2
Doubtful nycturia	40.02 or more	One normal in 56
	40.33 or more	One normal in 72
	40.64 or more	One normal in 93
	40.96 or more	One normal in 122
	41.28 or more	One normal in 162
	41.91 or more	One normal in 213
	41.59 or more	One normal in 286
	42.22 or more	One normal in 385
Nycturia	42.53 or more	One normal in 527
	42.85 or more	One normal in 740
	43.16 or more	One normal in 1,030

A. CONDITIONS

Constant Low Water Intake; Urea Administration.—The night urine was collected from 8 p. m. to 8 a. m. under the dietary conditions already given. The average percentage of urine volume and of urea to the twenty-four hour excretion was calculated for the fourth, fifth and sixth days, 20 gm. urea having been given at 8 a. m. on each of these days. There are twenty-eight observations.

The average percentage of the twenty-four hour urine volume excreted during the twelve hours of the night was 33.8 per cent.; the

standard deviation was ± 5.32 per cent., and the variability was 15.7 per cent. The odds for various percentages are given in Table 5.

The average percentage of the twenty-four hour urea excreted during the night was 33.4 per cent.; the standard deviation was ± 3.15 per cent., and the variability 9.4 per cent. Table 6 gives the odds.

C. CONDITIONS

Restriction of Water Intake; Urea Administration.—From 6 a. m. no fluids of any sort were taken, except that at 6 a. m. and at 6 p. m.

TABLE 7.—DEFINITION OF NYCTURIA

Volume of night urine as percentage of twenty-four hours' urine. Conditions: Restriction of water intake, urea administration.

Definition	Night Volume as Percentage of 24 Hours' Volume		Odds
No nycturia	43.0 or more	One normal in	2
Doubtful nycturia	53.46 or more	One normal in	56
	53.95 or more	One normal in	72
	54.45 or more	One normal in	93
	54.95 or more	One normal in	122
	55.45 or more	One normal in	162
	55.95 or more	One normal in	213
	56.45 or more	One normal in	286
	56.95 or more	One normal in	385
Nycturia	57.45 or more	One normal in	527
	57.95 or more	One normal in	740
	58.45 or more	One normal in	1,030

TABLE 8.—DEFINITION OF NYCTURIA

Urea in night urine as percentage of urea in twenty-four hours. Conditions: Restriction of water intake, urea administration.

Definition	Urea in Night Urine as Percentage of 24 Hours' Urea		Odds
No nycturia	52.2 or more	One normal in	2
Doubtful nycturia	62.08 or more	One normal in	56
	62.55 or more	One normal in	72
	63.00 or more	One normal in	93
	63.48 or more	One normal in	122
	63.95 or more	One normal in	162
	64.42 or more	One normal in	213
	64.90 or more	One normal in	286
	65.36 or more	One normal in	385
Nycturia	65.84 or more	One normal in	527
	66.30 or more	One normal in	740
	66.78 or more	One normal in	1,030

a solution containing 20 gm. urea in 200 c.c. of water was administered. There were thirty observations on twenty-three normal adults.

The average percentage of the twenty-four hour urine volume excreted during the twelve hours of the night was 43.0 per cent.; the standard deviation was ± 4.98 per cent.; the variability was 11.6 per cent. In Table 7 the odds are tabulated.

For the urea excretion the average was 52.2 per cent., with a standard deviation of ± 4.70 per cent. and a variability of 9.0 per cent. Table 8 gives the odds.

OBSERVATIONS ON PATIENTS WITH BRIGHT'S DISEASE

We have only scattered observations under most of the conditions outlined in the preceding section, but under both B and D conditions we have 113 volume measurements on the same group of eighty-six patients. These were an unselected, consecutively observed, group in all of whom measurement of the amount of effective renal tissue was made by means of the urea ratio test recently described.[2] Under B conditions the patient abstains from all fluids until next morning. The night urine from 6 p. m. to 6 a. m. is collected. Under D conditions the patient is given 1,000 c.c. of water with urea at 6 a. m. and drinks 500 c.c. of water every hour thereafter until 11 a. m. The largest of three hourly collections of urine made between 9 a. m. and 12 noon is taken. The volume obtained after restriction of fluids (B conditions) will be called the minimum volume, and the largest volume after water drinking

TABLE 9.—URINE VOLUMES COMPARED WITH UREA RATIOS

113 observations on 86 Patients. Average Percentage deviations from the normal average.

Diagnosis		Number of Observations	Maximum Volume, Percentage	Minimum Volume, Percentage	Urea Ratio Percentage
Glomerular nephritis	Diffuse	8	−64	± 0	−63
	Focal	22	−12	−16	−27
Nephrosis	Toxic	13	−15	− 3	−15
	Pregnancy	8	−27	−19	−25
	Cryptic	9	−45	−13	−48
	Pyogenic	6	−83	−79	−83
Renal arteriosclerosis		32	−26	− 6	−35
Renal sclerosis		15	−71	−104	−82

(D conditions) will be referred to as the maximum volume. We have thus in these patients an opportunity to compare the changes in urine volume under two diverse conditions with the changes in the amount of secreting tissue produced by the disease processes in the kidney. In Table 9 the cases have been classified in accordance with a system which will be described in a later paper. The average results of the three tests are given as ± percentage deviations from their respective normal averages, so that they are directly comparable.

As regards the maximum volume, Table 9 shows that it is less than normal in all forms of Bright's disease. In diffuse glomerular nephritis, in pyogenic nephrosis and in renal sclerosis the deficiency is very pronounced. If the maximum volume results are compared with the urea ratio results, it will be seen that in most cases there is a marked parallelism between the degree of reduction in urine volume and the degree of reduction in the amount of effective renal tissue. These, however, are average figures. The agreement in individual cases is, of course, much less close.

With the minimum volumes a very significant abnormality is found only in pyogenic nephrosis and in renal sclerosis and in both the volumes

are larger than normal. In these two groups the degree of increase in urine volume is not dissimilar from the degree of decrease in the urea ratio, but a considerable reduction in the amount of effective renal tissue can occur without any change in minimum volume, for in diffuse glomerular nephritis with a —63 per cent. ratio the minimum volume is normal.

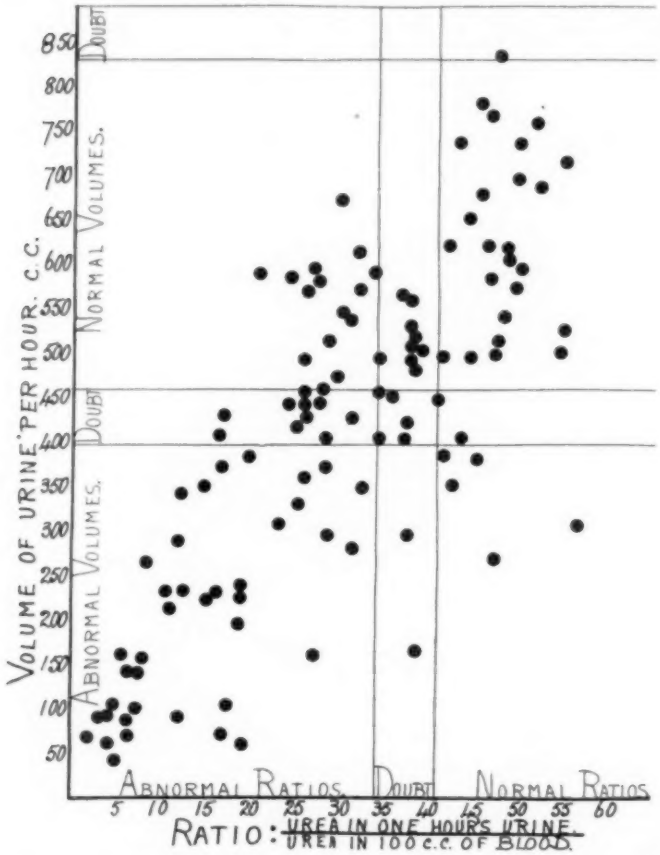

Fig. 1.—The relation between the maximum volume and the amount of secreting tissue in the kidney.

Some idea of the individual variation in the relation between urine volume and renal tissue changes can be obtained from Figures 1 and 2. The maximum and minimum volumes are plotted on the ordinates against the urea ratios on the abscissa. In each case the limits of normal, doubtful, and abnormal values are indicated.

Figure 1 shows that some patients with normal ratios may have abnormally low maximum volumes, and also that an abnormal ratio is not necessarily associated with an abnormal volume unless the ratio is very low.

Figure 2 shows that it is only in some cases with very low ratios that any definite abnormality in minimum volume is found.

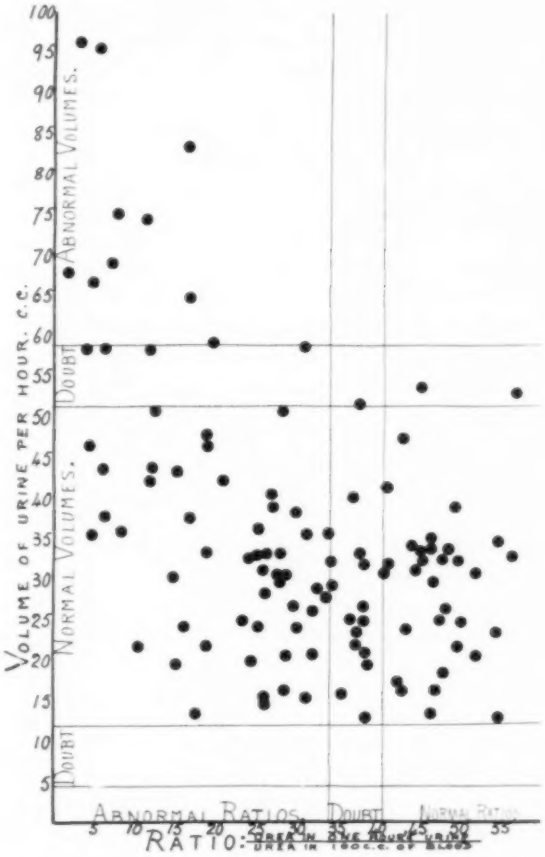

Fig. 2.—The relation between the minimum volume and the amount of secreting tissue in the kidney.

It was not to be expected that any close relation between urine volumes and urea ratios would be found because in a large number of our patients there were many other pathologic factors than a reduction in the size of the kidney which might have had an influence on the

urine volume. But all these many factors may be classified as extrarenal, and it may be said that all abnormalities in urine volume arise either from renal or from extrarenal causes or from both. The recognition of any special characteristics of abnormalities of urine volume due to renal causes which would allow of their separation from volume abnormalities due to extrarenal causes, would be of clinical importance from many points of view, especially, perhaps, because such a distinction would constitute a renal test of the utmost technical simplicity since nothing more than a measurement of urine volume would be needed. A consideration of the results obtained indicates that in some degree at least this distinction can be made.

When a patient has a urea ratio of 10 or less, his renal secreting tissue has been so extensively rendered functionless that we may be certain that his urine volumes have been influenced by purely renal causes. There is one respect in which the volume results in these low ratio cases differ from those observed in patients whose urea ratios are normal. When large amounts of water are given to patients whose kidneys are very much reduced in size, their maximum volumes are shown in Figure 1 to be considerably less than normal. On the other hand, when fluids are restricted, Figure 2 shows that their volumes tend to be greater than normal. A reversal in the direction of the abnormality when the conditions are reversed is thus a distinctive feature of abnormalities of urine volume in which renal causes are operative. The same fact is demonstrated in Table 9. The two forms of Bright's disease which have the most extreme reduction in the amount of renal tissue are pyogenic nephrosis and renal sclerosis. The maximum volumes of these groups are much less and their minimum volumes much greater than the normal average.

There is no such reversal of the direction of abnormality with change in the conditions in those patients whose kidneys have been only slightly, if at all, reduced in size, although such cases may show some degree of abnormality in either maximum or minimum volume. Thus in some cases the maximum volume may be low because the water which is given is retained for a long time in the stomach. But when the patient is given no fluids, the minimum volume is not found to be higher than normal. If a patient with edema happens to be unloading the retained fluid, his minimum volume may be too great, but when he is given large quantities of water to drink, his maximum volume will not be too small, it is, in fact, often larger than usual. Or, if a patient's tissues have an abnormal affinity for water, a considerable part of the water he takes may remain in his body, and his maximum volume may be too low. But unless there is an advanced renal lesion, his urine volume will not be too high when fluids are restricted; on the contrary, it is usually too low. Under diverse conditions extrarenal

causes tend to produce abnormalities in the same direction. Renal causes produce abnormalities in opposite directions.

It follows that when renal causes produce urine volume abnormalities, the quotient obtained by dividing the maximum volume by the minimum volume will be very low. This must be so because the dividend is decreased and the divisor is increased. When extrarenal causes are operative, the change in the volume quotient is less marked because if the dividend is decreased the divisor will remain normal or be decreased, or if the divisor is increased the dividend will remain normal or be

TABLE 10.—DEFINITION OF RELATION BETWEEN MAXIMUM AND MINIMUM URINE VOLUMES

The number of times by which the maximum volume exceeds the minimum volume.

Definition	Maximum Volume / Minimum Volume	Odds
Abnormally low	0.75 or less	One normal in 1,450
	1.4 or less	One normal in 1,000
	2.0 or less	One normal in 741
	2.6 or less	One normal in 527
Doubtful	3.2 or less	One normal in 385
	3.8 or less	One normal in 286
	4.4 or less	One normal in 213
	5.0 or less	One normal in 162
	5.6 or less	One normal in 122
	6.2 or less	One normal in 93
	6.8 or less	One normal in 72
	7.4 or less	One normal in 56
Normal	20.2 or less	One normal in 2
Doubtful	33.0 or more	One normal in 56
	33.6 or more	One normal in 72
	34.2 or more	One normal in 93
	34.8 or more	One normal in 122
	35.4 or more	One normal in 162
	36.0 or more	One normal in 213
	36.6 or more	One normal in 286
	37.2 or more	One normal in 385
Abnormally high	37.9 or more	One normal in 527
	38.4 or more	One normal in 741
	39.1 or more	One normal in 1,000
	39.7 or more	One normal in 1,450

increased. There is, therefore, good reason to believe that what we may call the volume quotient will be of value in distinguishing between renal and extrarenal causes of urine volume abnormalities.

Unfortunately, we do not have an adequate standard of normality for the volume quotient. Our standards for maximum and minimum volumes were obtained at different times on separate groups of normals, and since then we have been able to collect only thirty-two observations on thirty-one subjects. This is inadequate because the quotient necessarily carries the variability of both divisor and dividend, and a considerably larger number of observations should have been made. The average quotient was found to be 20.2 with a standard deviation of $\pm$ 6.08 and a variability of $\pm$ 30.2 per cent. The odds for various quotients are given in Table 10.

In Figure 3 the quotients of individual patients are plotted against the results of the urea-ratio test. No patients with normal ratios have abnormal quotients and no patients with a ratio of 10 or less have normal quotients.

The principle on which the volume quotient test is based is, I believe, a sound one, but it seems likely that the conditions used in carrying it

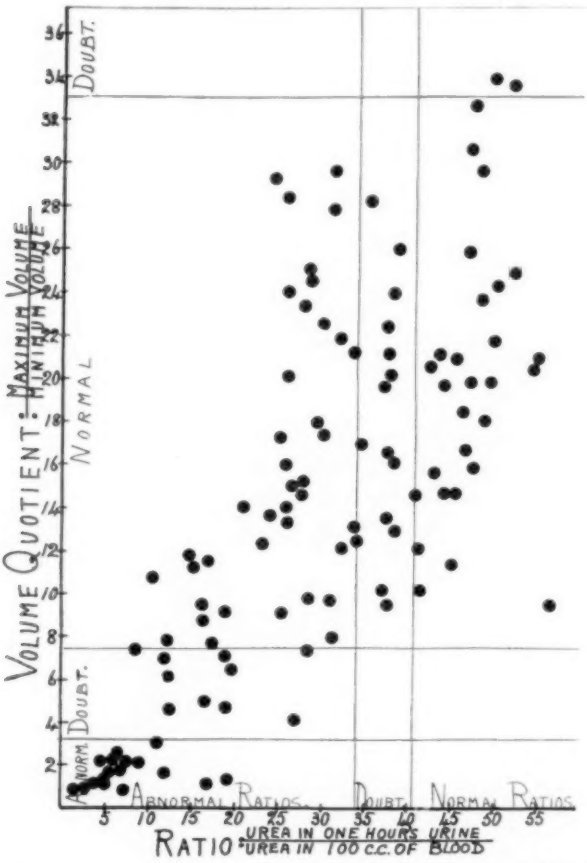

Fig. 3.—The relation between the volume quotient, i. e., $\frac{\text{maximum volume}}{\text{minimum volume}}$ and the amount of secreting tissue in the kidney.

out can be improved. This is the main reason why a more reliable standard of normality was not obtained. The normal "minimum" volume, especially, is highly variable and rarely approaches the true minimum. The variability is probably due, in the main, to differences

in the amount of "stored" water in the tissues of normal persons so that even after fluid restriction the night urine has still, in some cases, a considerable volume. If abstention from fluids were continued until the appearance of some such evidence of excess water depletion as a pronounced thirst, the volumes would probably be more constant and closer to the true minimum. But there are practical difficulties in that direction. The night urine is convenient and has a volume so considerable that errors from incomplete emptying of the bladder are probably not large. Certainly no short time collections would be feasible after fluid restriction. We are trying to find conditions which will combine convenience with a greater degree of strain and greater uniformity than our present method imposes. A properly conditioned volume quotient would be a useful renal test because it would have no technical difficulties of measurement and would in some degree free the physician from dependence on the laboratory.

There does not, however, seem to be any present prospect of a quantitatively accurate renal test based on urine volume measurements alone. It is true that water can be ingested in much larger quantities than can any other substance, and if it were possible to get so large an amount into the blood that the water excreting capacity of the kidneys were overtaxed, we might expect to find a direct relationship between the amount of secreting renal tissue and the magnitude of the volume of urine excreted during a given time. But experiments with rabbits have convinced us that the renal capacity cannot be overtaxed by any amount of water it is at all practical to administer. We are thus obliged to measure the amount of water in the blood. But even when a pronounced diuresis has been induced by water drinking, the increase in the total water content of the blood is slight. This fact has been reemphasized by Haldane and Priestley [3] and we have made the same observation. It is only that relatively small part of the total water of the blood which is available for excretion by the kidney which should be measured, but we have no means of determining the amount of this fraction alone. Until such a method has been developed, it is not possible to determine the ratio between the water in the urine and the free water in the blood, the figure which, if it were obtained under appropriate conditions, would probably give the most accurate indication of the water excreting capacity of the kidneys and would bear the closest relation to the amount of renal secreting tissue.

CONCLUSIONS

1. The terms oliguria, polyuria and nycturia have been statistically defined by reference to the distribution of urine volumes and of urea

3. Haldane and Priestley: J. Physiol. **50**:296, 1916.

excretion found in normal adult subjects under fixed conditions designed to put a strain on the water and urea excreting capacity of the kidney.

The following distributions were found:

OLIGURIA AND POLYURIA

Conditions	Average Cubic Centimers	Standard Deviation Cubic Centimers	Variability Per Cent.
A	1345	±178.0	13.2
B	381	±112.5	29.5
C	639	±153.5	24.0
D	643	± 88.	13.7

NYCTURIA

1. Volume of Urine

Conditions	Average Per Cent.	Standard Deviation Per Cent.	Variability Per Cent.
A	33.8	±5.32	15.7
C	43.0	±4.98	11.6

2. UREA

Conditions	Average Per Cent.	Standard Deviation Per Cent.	Variability Per Cent.
A	33.4	±3.15	9.4
C	52.2	±4.70	9.0

2. Abnormalities in urine volume which are due to renal causes are characterized by the fact that with a large intake of water the volumes are too small, while with a small intake of water the volumes are too large. Extrarenal causes do not produce this reversal of the direction of abnormality when the conditions are changed.

3. In those cases in which renal causes of urine volume abnormality are predominant, the quotient obtained by dividing the volume per hour when a large amount of water has been taken by the volume per hour when fluids are restricted is much less than the normal average, whereas, when extrarenal causes are operative, the quotient deviates to a lesser degree, if at all, from the normal.

STUDIES ON THE PHYSIOLOGY OF THE LIVER

IV. THE EFFECT OF TOTAL REMOVAL OF THE LIVER AFTER PANCREATECTOMY ON THE BLOOD SUGAR LEVEL *

FRANK C. MANN, M.D., AND THOMAS B. MAGATH, M.D.

ROCHESTER, MINN.

Previous reported studies [1] on the physiology of the liver have demonstrated that (1) a characteristic group of symptoms followed by death develops after total removal of the liver; (2) these symptoms are associated with decreasing blood sugar, and the various symptoms and death occur at definite blood sugar levels; (3) the injection of glucose after symptoms develop abolishes them and restores the animal to normal, and (4) if glucose is administered after hepatectomy in amounts sufficient to maintain the blood sugar level at normal or above normal, the characteristic symptoms do not develop, but the animal lives for a variable period of time, which is always much longer than if glucose had not been administered, and dies following the development of a totally different group of symptoms.

These striking and very definite results have proved that the maintenace of the normal level of blood sugar is absolutely dependent on the liver. Furthermore, there is a certain critical level of blood sugar below which it is impossible for the organism to live. The liver thus assumes renewed importance and undoubtedly has a vital function as regards carbohydrate metabolism.

Since the classical experiments of Mering and Minkowski [2] it has been known that total pancreatectomy produces glycosuria. Many investigators have demonstrated that hyperglycemia follows total removal of the pancreas. This effect has been attributed to an internal secretion of the island tissue of the organ. The experiments of Banting and Best,[3] working in MacLeod's laboratory, have greatly strengthened this internal secretion theory.

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* From the Division of Experimental Surgery and Pathology, and the Section on Clinical Laboratories, The Mayo Foundation.

1. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver. II. The Effect of the Removal of the Liver on the Blood Sugar Level, Arch. Int. Med. **30**:73-84 (July) 1922. Studies on the Physiology of the Liver. III. The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, Arch. Int. Med. **30**:171-181 (Aug.) 1922.

2. Mering, J., and Minkowski, O.: Diabetes mellitus nach Pankreasextirpation, Arch. f. exper. Path. u. Pharmakol. **26**:371-387, 1889.

3. Banting, F. G., and Best, C. H.: The Internal Secretion of the Pancreas, J. Lab. & Clin. M. **7**:251-266, 1922. Pancreatic Extracts, J. Lab. & Clin. M. **7**:464-472, 1922.

It is evident, therefore, that the two glands, liver and pancreas, have a reciprocal action on the concentration of sugar in the blood. When the liver is removed the sugar disappears from the blood; when the pancreas is removed the sugar increases in the blood. The decrease of blood sugar following hepatectomy is associated with definite and characteristic symptoms leading to death a few hours after the loss of liver function. The increase of blood sugar following pancreatectomy is also associated with definite symptoms, but death does not occur until several days or weeks after the loss of the pancreas. It became an important phase of our problem on the relation of the liver to carbohydrate metabolism to determine which effect would be pro-

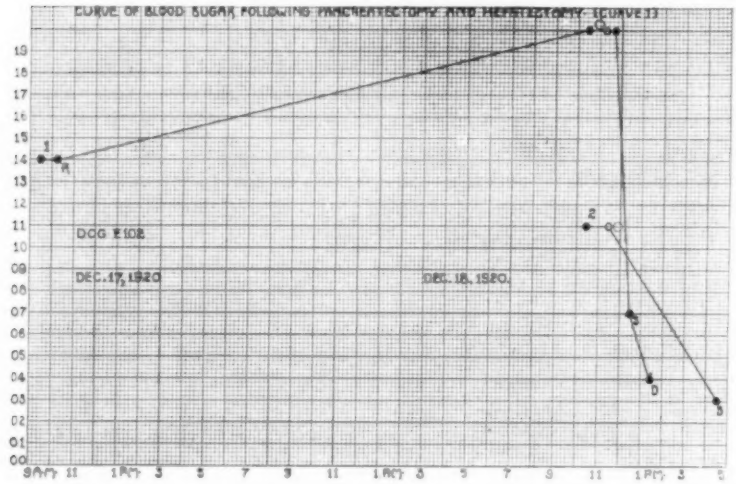

Fig. 1.—Curve 1: At *R* the pancreas was removed. Blood sugar increased but not as much as is usually noted. *O* (twenty-four hours later), liver removed. The blood sugar decreased rapidly. *S*, characteristic symptoms developed, and *D*, the animal died. Curve *2*: The average curve of blood sugar following hepatectomy. *O*, liver removed; *S*, characteristic symptoms.

duced on the blood sugar level by the removal of both glands at varying intervals in relation to each other. It was essential to determine whether the liver was necessary for the hyperglycemia following pancreatectomy, and whether the pancreas played an important part in the hypoglycemia following hepatectomy.

While many investigations on the effect of hepatectomy and pancreatectomy have been made, few of them have included a study of the effect of removal of the two glands in relation to each other and to the blood sugar content. The work of the first investigators on

hepatectomy in mammals (Bock and Hoffman,[4] Schenck,[5] Tangl and Harley[6]) has a bearing on the problem only as regards the fact that the technic which they employed in removing the liver in many instances must have also greatly damaged the circulation to the pancreas. In those experiments in which the circulation was restricted to the anterior portion of the body (Seegen,[7] Kaufmann[8]) both the liver and pancreas were functionally removed. In the experiments in which

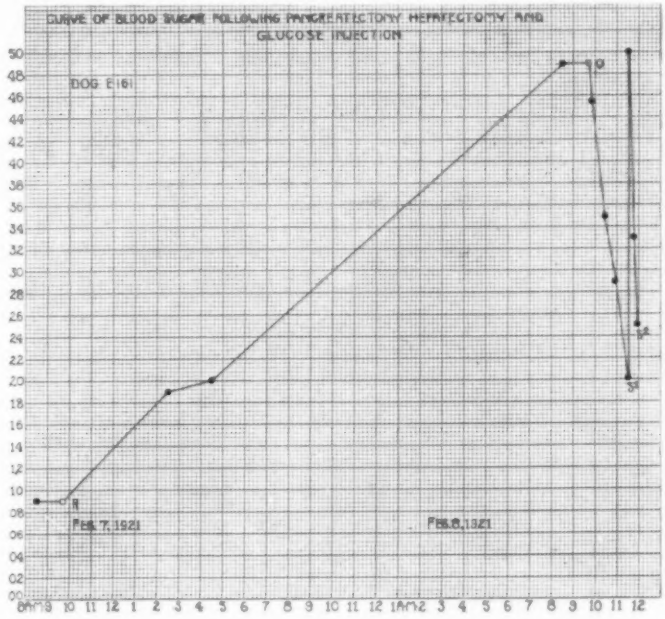

Fig. 2.—*R*, pancreas removed. *O* (forty-eight hours later), liver removed: *S*, characteristic symptoms. An injection of glucose was given. The animal was restored to normal for a short time but at S^2 symptoms again appeared. Note the increase in blood sugar following pancreatectomy, the subsequent decrease following hepatectomy and the development of symptoms with a blood sugar above normal.

4. Bock, C., and Hoffmann, F. A.: Experimental Studien über Diabetes, Berlin, H. E. Oliven, 1874.

5. Schenck, F.: Ueber den Zuckergehalt des Blutes nach Blutentziehung, Arch. f. d. ges. Physiol. **57**:553-572, 1894.

6. Tangl, F., and Harley, V.: Beitrag zur Physiologie des Blutzuckers, Arch. f. d. ges. Physiol. **61**:551-559, 1895.

7. Seegen, J.: Die Zuckerbildung im Thierkörper, ihr Umfang und ihre Bedeutung, Berlin, A. Hirschwald, 1890.

8. Kaufmann, M.: Nouvelles recherches sur la pathogenie du diabète pancréatique, Compt. rend. Acad. d. sc. **118**:656-659, 1894.

evisceration was employed, (Kaufmann,[9] Pavy and Siau [10]), the pancreas might or might not have been damaged. It is obvious that such experiments are necessarily very short and offer no opportunity to note symptoms and make other observations. It should be noted, however, that in all of these experiments a decrease in blood sugar was found.

Hédon [11] seems to have been the first to remove the liver from dogs after previously performing pancreatectomy. His results are inconclusive.

Kaufmann [9] removed different portions of the viscera in normal and pancreatectomized dogs and observed the blood sugar. He was not successful in removing the entire liver and the animals were maintained

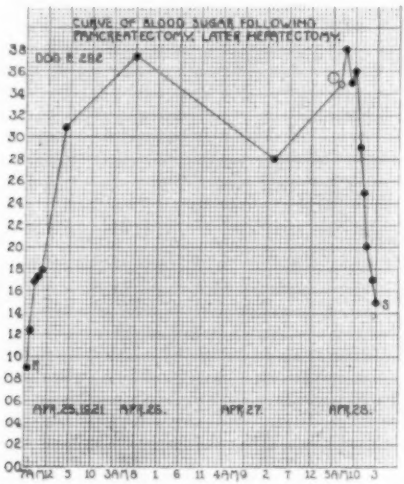

Fig. 3.—Curve of blood sugar following pancreatectomy, later hepatectomy. *R*, pancreas removed; *O* (seventy-two hours later), liver removed. *S*, characteristic symptoms.

under chloroform anesthesia. He records a decrease in blood sugar in both normal and pancreatectomized animals.

Marcuse [12] removed the pancreas from frogs and noted a marked glycosuria. He then removed the pancreas and liver simultaneously from the same species of animal and no glycosuria was observed.

9. Kaufmann, M.: De l'influence exercée par la suppression partielle ou totale de la fonction hépatique sur la glycémie chez les animaux normaux et diabétiques, Arch. de physiol. norm. et path. **8**:151, 1896.

10. Pavy, F. W., and Siau, R. L.: The Influence of Ablation of the Liver on the Sugar Content of the Blood, J. Physiol. **29**:375-381, 1903.

11. Hédon, E.: Sur la pathogénie du diabete consécutif à l'extirpation du pancréas, Arch. de physiol. norm. et path. **4**:245-258, 1892.

12. Marcuse, W.: Ueber die Bedeutung der Leber für das Zustandekommen des Pankreas-diabetes, Ztschr. f. klin. Med. **26**:225-257, 1894.

Kausch [13] has made the most extensive investigation of the blood sugar following removal of both the liver and pancreas. He employed geese and ducks. He first removed the liver of a series of normal fowls in a manner similar to Minkowski,[14] and obtained identical results with respect to symptoms and decrease in blood sugar following hepatectomy. He then removed the liver from fowls from which the pancreas had been removed from twelve to forty-eight hours previously. He found that the blood sugar decreased even more rapidly in the fowls which had been pancreatectomized preceding the hepatectomy. He also noted that the pancreatectomized birds had less glycogen in the muscle than the normal controls and considers this decrease in the reserve

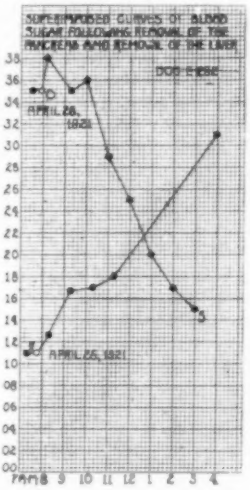
SUPERIMPOSED CURVES OF BLOOD SUGAR FOLLOWING REMOVAL OF THE PANCREAS AND REMOVAL OF THE LIVER
DOG 5 BSE
APRIL 26, 1921
APRIL 25, 1921
P.M. 8 9 10 11 12 1 2 3 4

Fig. 4.—This curve is composed of the two portions of the curve in Figure 3 in order to illustrate the reciprocal action of the liver and pancreas as regards blood sugar. The removal of the pancreas, *R*, produces an immediate increase in blood sugar, while removal of the liver produces an equally characteristic decrease.

supply of carbohydrate the cause for the more precipitate decrease in blood sugar when both glands were removed.

MacLeod and Pearce [15] studied the results of disappearance of sugar in eviscerated dogs, normal animals and those previously pancrea-

13. Kausch, W.: Der Zuckerverbrauch im Diabetes mellitus des Vogels nach Pankreasextirpation, Arch. f. exper. Path. u. Pharmakol. **39**:219-244, 1897.

14. Minkowski, O.: Ueber den Einfluss der Leberextirpation auf den Stoffwechsel, Arch. f. exper. Path. u. Pharmakol. **21**:41-87, 1886.

15. Macleod, J. J. R., and Pearce, R. G.: The Sugar Consumption in Normal and Diabetic (Depancreated) Dogs After Evisceration, Am. J. Physiol. **32**:184-199, 1913. Further Observations on the Rate at Which Sugar Disappears from the Blood of Eviscerated Animals, Am. J. Physiol. **33**:378-381, 1914.

tectomized. While their results were quite variable, they obtained a decrease in blood sugar in both series of experiments. It should be noted that such experiments necessarily require the continuous use of anesthetics or other means of maintaining unconsciousness.

A survey of the previous work on the blood sugar level following removal of both liver and pancreas shows that a decrease has almost invariably occurred. However, with the exception of the experiments on ducks and geese in which the portal system anastomoses with the systemic venous system, the results of the experiments were not conclusive.

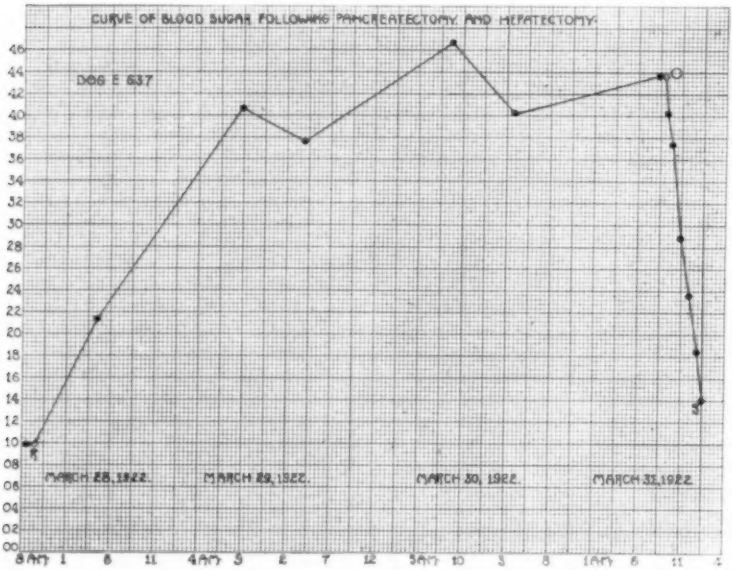

Fig. 5.—Curve of blood sugar following pancreatectomy and hepatectomy. *R*, pancreas removed; *O* (ninety-six hours later), liver removed. *S*, characteristic symptoms developed.

METHOD OF EXPERIMENTATION

All of our operations were performed under ether anesthesia and with sterile technic. The animals (dogs) were prepared for removal of the liver by the two preliminary operations previously described. The pancreas was then removed, employing the usual technic. At varying periods of time after pancreatectomy the liver was removed. The blood sugar was estimated at varying intervals throughout the experiment. After pancreatectomy the animals were given a milk diet. The methods employed for obtaining blood specimens and estimation of blood sugar were the same as those previously described.

Total Removal of the Liver and Pancreas at the Same Time.—When the pancreas and liver are removed at the same operation the resultant condition is the same as though only the liver had been removed. The blood sugar decreases, and associated with this decrease, the characteristic symptoms which follow hepatectomy develop. The curve of blood sugar is the same as when the liver alone is removed. The injection of glucose restores the animal to normal. Usually the animal does not live as long after operation as when only the liver is removed, but otherwise the pancreatectomy does not seem to exert any effect on the resulting condition.

Total Removal of the Liver from Twenty-Four to Forty-Eight Hours After Pancreatectomy.—The blood sugar level is usually from two to four times greater than normal, from twenty-four to forty-eight hours after total pancreatectomy. When the liver is removed at this time the decrease in blood sugar takes place immediately and is

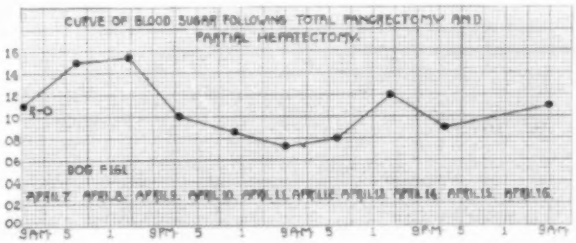
CURVE OF BLOOD SUGAR FOLLOWING TOTAL PANCREATECTOMY AND PARTIAL HEPATECTOMY.
16
14
12
10
08
06
04
02
00
R-O
DOG F 151
APRIL 7 APRIL 8 APRIL 9 APRIL 10 APRIL 11 APRIL 12 APRIL 13 APRIL 14 APRIL 15 APRIL 16
9AM 5 1 9PM 5 1 9AM 5 1 9PM 5 1 9AM

Fig. 6.—Curve of blood sugar following total pancreatectomy and partial hepatectomy. This curve is a continuation of the curve given in Figure 7. At *R-O* the pancreas and approximately 40 per cent. of the liver were removed. Note that the blood sugar remained almost normal during the succeeding days, although the animal was on a milk diet and developed the other characteristics of a pancreatectomized animal.

most marked. The characteristic symptoms associated with hepatectomy develop, but they appear earlier than if only the liver has been removed and usually appear at a much higher blood sugar level. The animal is restored to normal by the injection of glucose, but it soon develops symptoms again and dies within a few hours after removal of the liver.

Total Removal of the Liver from Forty-Eight to Ninety-Six Hours After Pancreatectomy.—The blood sugar level usually remains fairly constant at from four to five times above normal from forty-eight to ninety-six hours after total removal of the pancreas. When the liver is removed during this interval, folowing pancreatectomy, the decrease in blood sugar takes place immediately and is most marked. Within two hours after hepatectomy the characteristic symptoms appear, but

they develop at a blood sugar level which, although considerably below the preoperative level, is still above normal. The injection of glucose produces a fleeting restorative reaction but the animal soon passes into coma and dies.

Total Removal of the Liver More than Ninety-Six Hours After Pancreatectomy.—Coma has followed the anesthesia and operative procedure of hepatectomy in all animals in which the liver was removed more than ninety-six hours after total pancreatectomy.

Partial Removal of the Liver Before and After Pancreatectomy.—As our results indicated that the hyperglycemia following pancreatectomy was dependent on the presence of the liver, it seemed desirable

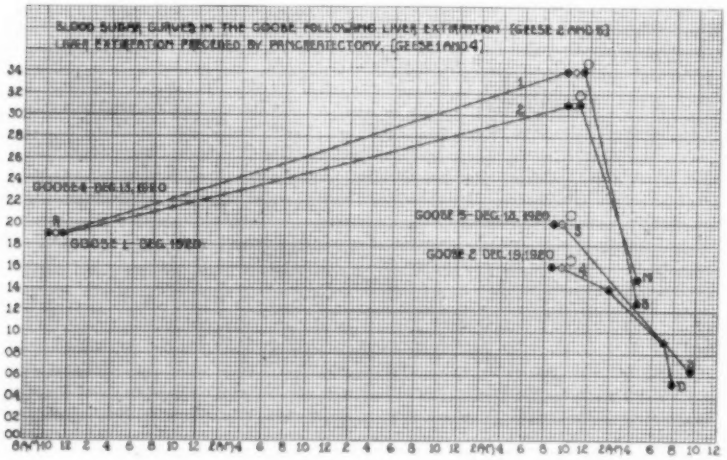
BLOOD SUGAR CURVES IN THE GOOSE FOLLOWING LIVER EXTIRPATION (GEESE 2 AND 5)
LIVER EXTIRPATION PRECEDED BY PANCREATECTOMY. (GEESE 1 AND 4)
GOOSE 4 DEC. 13, 1920
GOOSE 1 DEC. 1920
GOOSE 5 DEC. 12, 1920
GOOSE 2 DEC. 13, 1920

Fig. 9—*R*, pancreas removed; *O*, liver removed; *N*, normal; *S*, characteristic symptoms; *D*, fowl died.

to determine whether a partial removal of the liver would affect the change in blood sugar level following pancreatectomy. In the first experiments we removed the pancreas from normal dogs, and a few days later, when a marked hyperglycemia had developed, various portions of the liver were removed. Subsequent to the partial hepatectomy the blood sugar decreased but did not return to a normal level. The totally pancreatectomized animal did not withstand the subsequent operation well and the results of the experiments were inconclusive. In the next series of experiments, portions of the liver were removed at the same time as the pancreas. The hyperglycemia resulting from the pancreatectomy was not so great, but otherwise the same results were noted as when the liver was left intact.

It has been emphasized by our previous experiments and those of other investigators, that only a small portion of the normal liver is necessary for the maintenance of its function. In a previous article [16] we reported a method for producing chronic insufficiency of the liver. Briefly, the method consists in removing a portion of the liver of an animal in which an Eck fistula has been made a considerable time before. Such a liver does not seem capable of regenerating to any great extent and consequently its function can be greatly reduced.

We, therefore, tried removing the pancreas and a portion of the liver from an animal in which an Eck fistula had been made several weeks before. Total removal of the pancreas and partial removal of the liver in such an animal does not produce marked changes in blood sugar. In fact, in one animal the blood sugar remained within normal limits for ten days after operation and there was no glycosuria, although the animal exhibited the general appearance of having been pancreatectomized.

DISCUSSION

The results of the experiments are very definite as regards the liver, and their interpretation seems evident. They prove conclusively that the liver is absolutely necessary for the maintenance of the blood sugar level in the hyperglycemic animal in the same manner as in the normal animal. The increase in blood sugar following pancreatectomy is dependent on the presence of the liver. Without an adequate amount of functionating liver tissue, the increase in blood sugar following pancreatectomy could not occur. We have thus proved in another way that whatever may be the process of carbohydrate metabolism, the liver has a vital part in that process.

The results of the experiment with regard to the pancreas are not so clear. They do not show why the loss of the pancreas should cause the rise in the blood sugar, but they do prove that the presence of the liver is necessary for this rise. It is evident that the decrease in blood sugar in the pancreatectomized animal following hepatectomy is due to the total loss of the mechanism for supplying this sugar, but what becomes of the sugar in the blood of the pancreatectomized and hepatectomized animal if it is not utilized is not so evident. The sugar was not eliminated by way of the kidneys because many of the animals were anuric after hepatectomy, and those that did secrete urine passed only a small amount of sugar after operation. It is possible, but not probable, that enough of the internal secretion of the pancreas was present after pancreatectomy to account for the decrease after hepa-

16. Mann, F. C., and Magath, T. B.: The Production of Chronic Liver Insufficiency, Proc. Am. J. Physiol. **59**:485, 1922.

tectomy. Another point of interest is the observation that the characteristic symptoms following hepatectomy occur at a much higher blood sugar level when the pancreas has been removed some time before.

SUMMARY

The liver and pancreas were removed at varying intervals in relation to each other. When the two glands were removed at the same time, the resulting condition was the same as though only the liver had been removed. When the liver was removed from twenty-four to ninety-six hours after pancreatectomy, the blood sugar decreased quickly and the same characteristic symptoms developed as after hepatectomy, but at a higher blood sugar level. The injection of glucose restored the animal to a normal state, but the effect of the glucose was transitory. The total removal of the pancreas and partial removal of the liver in an animal in which an Eck fistula had been made was followed by only slight or no increase in blood sugar. These experiments prove that the presence of the liver is absolutely necessary for the hyperglycemia following pancreatectomy.

THE PRODUCTION OF URINARY CALCULI BY THE DEVITALIZATION AND INFECTION OF TEETH IN DOGS WITH STREPTOCOCCI FROM CASES OF NEPHROLITHIASIS*

EDWARD C. ROSENOW, M.D., AND JOHN G. MEISSER, D.D.S.
ROCHESTER, MINN.

Infection is regarded as a common cause of calcification in tissues, but the hypothesis that certain microorganisms which infect man may have peculiar power in this respect is not generally believed. It was suggested to one of us during experiments with a streptococcus isolated from an excised piece of muscle in a case of calcifying myositis. This strain was peculiar, in comparison with strains of streptococci from the more common forms of myositis, in that it not only produced marked lesions in the muscles of rabbits when injected intravenously, but also produced very early precipitation of calcium salts in the lesions.[1] The etiologic relationship of streptococci to the formation of gallstones was demonstrated by one of us a number of years ago in experimental cholecystitis produced by intravenous injection of streptococci from cholecystitis in man.[2]

During the preparation of immune serums, in which repeated intravenous injections of dead streptococci having different localizing powers were made, numerous concretions were found at necropsy in the calices and substance of the kidneys (Fig. 1) of the sheep injected with a pyelonephritis strain; no other lesions were found.

In a series of experiments in which nephritis followed the devitalization and infection of teeth in dogs with a staphylococcus from a case of nephritis, one dog developed pyelitis and cystitis, with marked calcareous deposits in the adherent exudate in the pelvis of the kidney and in the bladder.[3]

On the basis of these observations it was believed to be worth while to attempt to produce urinary calculi in dogs by creating foci of infection around the teeth with organisms isolated from the urine and foci of infection in persons suffering from nephrolithiasis, thus simulating the conditions so often present in patients. In this paper we shall report the results obtained in a series of experiments with the streptococci

* From the Division of Experimental Bacteriology, The Mayo Foundation.

1. Rosenow, E. C., and Ashby, Winifred: Focal Infection and Elective Localization in the Etiology of Myositis, Arch. Int. Med. **28**:274 (Aug.) 1921.

2. Rosenow, E. C.: The Etiology of Cholecystitis and Gallstones and Their Production by the Intravenous Injection of Bacteria, J. Infect. Dis. **19**: 527, 1916.

3. Rosenow, E. C., and Meisser, J. G.: Elective Localization of Bacteria Following Various Methods of Inoculation, and the Production of Nephritis by Devitalization and Infection of Teeth in Dogs, J. Lab. & Clin. M. **7**:707, 1922.

isolated from typical examples of this disease, a study made possible through the cooperation of Dr. Braasch and his associates, of the section on urology in the Mayo Clinic.

METHOD OF STUDY

Cultures from the catheterized urine of the patients and from foci of infection in tonsils and teeth were made on blood-agar and in tall tubes of glucose-brain broth. The primary culture in glucose-brain broth, containing a pure growth or a preponderance of the streptococci, was usually first inoculated intravenously into rabbits. If lesions of the urinary tract, usually of the medulla of the kidneys, developed, from which the streptococcus could be isolated, the teeth of dogs were inoculated with this strain. In some instances the teeth of dogs were

Fig. 1.—Photograph of a colored drawing of the kidney of a sheep showing concretions following repeated intravenous injections of a dead streptococcus from pyelonephritis (× ¾).

infected with the primary culture directly from the foci of infection or from the urine of the patient.

The dogs selected were active and well nourished. Catheterized specimens of urine were normal, and roentgenograms of the kidneys, ureter and bladder were negative at the beginning of the experiments. In devitalizing and infecting the teeth, the animals were covered with a sterile sheet, and kept under ether anesthesia by the intratracheal method. A rubber dam was used to isolate the teeth to be worked on. The teeth were scrubbed, and sterilized with alcohol and tincture of iodin, then cut off with sterile bone nippers midway between the incisal edge and the gum margin. The pulp canal was drilled into with sterile dental drills. The pulps were removed with sterile broaches, and after the hemorrhage had ceased, the bacteria, in dense suspension, were introduced into the pulp chambers with fine capillary glass pipets. The canals

were then sealed with impervious dental cement or amalgam. In most instances three cuspids were infected; in a few cases, only the two lower cuspids were infected; and in order to determine whether the streptococci from these artificially produced foci, or bacteria from other sources might localize and produce periapical infection around teeth from which the pulp had been removed, the fourth cuspid was devitalized, but not infected. The animals were numbered and weighed; they were kept under hygienic conditions and fed a balanced ration of dog biscuit, occasionally supplemented by meat. A supply of water rich in lime salts was constantly before them. Catheterized specimens of urine were examined at intervals. In from fifty-one to 120 days after the infection of the teeth, one kidney was removed from each dog by Dr. Williamson. This afforded opportunity at necropsy some time later to compare the findings in that kidney with those of the opposite kidney.

Various tests were made to prove the causal relationship of the streptococci in the experimentally induced foci of infection to the lesions in the urinary tract and the formation of renal calculi. Cultures were made from the infected teeth, urine, kidneys and renal calculi in the dogs. The localizing power of the freshly isolated cultures was determined by intravenous injection into rabbits. Painstaking search was made for the organism in the lesions in the kidneys and in, or adjacent to, areas in which sections revealed beginning stone formation.

In studying the localizing power of the strains isolated from the patients and from the dogs whose teeth were infected, from 3 to 5 c.c. of the primary culture in glucose-brain broth was injected intravenously into rabbits of medium size. In some instances young cultures in the second to the fourth rapidly made subculture were injected. Search for focal lesions of the viscera, including the medulla of the kidney, was made immediately in the animals anesthetized for examination in from two to seven days after injection, and as soon after death as possible in those animals that died as the result of the injection. The urine was cultured and examined for albumin, casts, pus and blood. Cultures from the kidneys of the dogs and rabbits were usually made from small amounts of the pipetted substance of the kidney, occasionally from large portions macerated in a mortar, from the teeth with the pipetted material from the pulp chamber and infected area in the periapical region, and from the crushed calculi after repeated washings in sterile salt solution. The tissues were fixed in 10 per cent. formaldehyd solution and imbedded in paraffin. Sections were stained for lesions with hematoxylin and eosin, for bacteria by the Gram method, and treated by von Kossa's silver nitrate method to prove that the deposits in the kidneys which stained deeply with hematoxylin contained lime salts.

Nine cases of nephrolithiasis were studied. In order best to illustrate the results obtained, we shall give detailed experiments in the first case studied, and a summary of the results of all the cases.

HISTORY OF CASE

History.—A physician, aged 34 years, had repeated attacks of renal colic for four years previous to our investigation. The first attack occurred about six months after an attack of pansinusitis, in which there was marked prostration, fever and pain for three weeks, followed by slow recovery. For several years the attacks of colic occurred only during the cold months, and at first were thought to be due to gallstones, but later they proved to be due to stones in the right kidney. In the autumn of 1918, six months after his attack of sinusitis, a rough stone, somewhat larger than a wheat grain, was passed. This was followed by hematuria and the passage of blood clots, and at times dull pain in the right loin, and abdomen, but there was no colic for twenty-three months. October, 1920, after heavy lifting, he had an attack of marked weakness, followed by hematuria. The hematuria recurred for two days, and for six weeks he had many attacks of severe colic.

Examination.—Cystoscopic and roentgen-ray examinations revealed an impacted stone in the right ureter, 10 cm. from the bladder.

Treatment.—This calculus was removed by Dr. Judd Nov. 27, 1920. The stone was extremely hard and consisted largely of calcium carbonate. Convalescence was uneventful and the patient was free from renal symptoms for three months, when they recurred. In March, 1921, he passed five soft stones. He then had intermittent attacks for several months. September 28, he had severe colic, followed by chills and fever.

From June 23 to August 5, 1921, the patient was given seven subcutaneous injections of a lipovaccine prepared from the strain of streptococcus that was inoculated into the teeth of the dogs. The dose varied from 340 to 960 millions of streptococci. He had no constitutional reaction, and there was no change in the number and severity of attacks.

From Nov. 10, 1920, to Oct. 21, 1921, six infected teeth were removed in four sittings. All of these had been rendered pulpless some years before. One tooth, which gave symptoms of a dying pulp, was removed by simple extraction Oct. 21, 1921. Severe constitutional reaction followed within five hours and lasted for several days. Our experiments were performed with cultures from this tooth.

Lavage of the kidneys, prolonged rest and forced feeding, especially with large quantities of milk, were instituted after extraction of the last infected tooth. During six weeks the patient gained twenty pounds, and remained free from urinary symptoms until June 1, 1922, when, after a long automobile trip, he developed pain and tenderness around the teeth in the upper jaw on the left side, the result of acute infection of the left antrum. During this attack the patient developed colic and hematuria, but was not aware of passing a stone. After the acute symptoms had subsided, the antrum was irrigated on two occasions; the urine was kept neutral or alkaline by the administration of sodium bicarbonate for several months, and the patient was free from urinary symptoms for five months.

Bacteriologic Examination.—During the attacks of colic the urine usually contained pus, gross or microscopic blood, relatively few casts, and a small amount of albumin. In quiescent intervals only a few leukocytes were found, but during attacks, many were found, and always a moderate increase in the amount of mucin. Smears from the sediment and from the flakes of mucus yielded short-chained streptococci and staphylococci. Blood-agar-plate cultures from the sediment of catheterized specimens, from the bladder and from the kidney, yielded a variable number of small, dry, usually nonadherent colonies

of streptococci, surrounded by a narrow greenish zone, often with slight hemolysis peripheral to this zone, and a small number of larger, opaque, grayish, indifferent colonies of staphylococci. The growth in glucose-brain broth was usually granular, often with spontaneous precipitation in from twenty-four to forty-eight hours. Smears yielded long and short chains of elongated, nonencapsulated, gram-positive diplococci, varying considerably in size. Blood-agar plate cultures from the broth, and directly from the urine, yielded the two types of colonies described, the green colonies of streptococci always predominating in number. The morphology of the organisms, and the colonies on blood-agar resembled *Streptococcus viridans*. At times it was difficult to differentiate the staphylococci from isolated diplococci, or from diplococci in clumps. Moreover, large and small coccus forms occurred in chains consisting otherwise of typical elongated diplococci.

EXPERIMENTAL OBSERVATIONS

The primary culture in glucose-brain broth from the tooth extracted Oct. 21, 1921, following which the patient had a reaction, was injected into four rabbits. All appeared well forty-eight hours after the injection, when they were anesthetized. All had mild lesions in the kidneys, chiefly of the medulla, and two also had hemorrhages of the bladder, but were otherwise free from lesions. A small amount of albumin, blood and pus cells was found in the urine of three rabbits. The culture of a lymphoid tag from a tonsillectomy scar produced lesions in the medulla of the kidneys of two rabbits injected intravenously; in one rabbit, hemorrhages and infiltration of the bladder, and arthritis also developed.

The localizing power of the culture from the urine was tested by intravenous injection into rabbits on seven occasions over a period of one and a half years. Twenty-four rabbits were injected; two died, and the others were chloroformed in from two to eight days. Lesions of the kidneys, chiefly of the medulla, were found in thirteen of the animals, of the kidneys and bladder in one, and of the urinary bladder, without lesions in the kidneys, in two. Lesions of the urinary tract developed in sixteen rabbits (66 per cent.). Other tissues were free from lesions, with the exception of a few hemorrhages in the muscles of two of the rabbits.

Of the total of thirty rabbits injected with cultures from teeth, tonsillar tag and urine, twenty-three (77 per cent.) developed lesions in the urinary tract, twenty-one developed lesions of the kidney, six of which also had lesions in the urinary bladder, and two developed lesions of the bladder only.

Intravenous injection of seventeen rabbits with the streptococcus obtained from the teeth of the dogs used in this case produced mild lesions of the medulla of the kidneys in twelve; two of these rabbits also had slight hemorrhages in the bladder, and turbidity of joint fluid; one rabbit had hemorrhages of the bladder without lesions of the kidney, and two rabbits were free from lesions. All the animals survived and were anesthetized in from two to four days after injection.

Four series of experiments were performed on dogs in this case. Three series of dogs were inoculated with cultures isolated from the urine, and one series was inoculated with cultures from an infected tooth.

In the first series the teeth of two dogs were devitalized and infected directly with the primary culture from the urine. Both dogs developed calculi. One dog died of distemper forty-six days later. The kidneys and bladder contained a large number of small, hard calculi; the stones in the kidney were often loosely adherent to the mucous membrane of the calices. The left kidney of the second dog was removed on the fifty-first day. It contained grayish-white linear streaks and small con-

Fig. 2.—Kidney of a dog showing stones in the pelvis, an impacted stone in the ureter, dilatation of the pelvis, and "ascending" nephritis (×1).

cretions in the medulla. The operation wound healed without suppuration, but the animal lost in weight, despite the fact that it ate normally. Later it become inactive, and lost much of its hair. It died seemingly of inanition on the seventy-ninth day. The right kidney was congested, contained large and small, white, almost necrotic areas, often wedge-shaped in the medulla and of irregular shape in the cortex. The capsule stripped readily. The cortex was swollen; the cortical markings were distinct. The pelvis was distended with whitish mucopurulent material in which large, yellowish, angular, rough calculi were embedded (Fig. 2). The shape of some conformed to the calices in which they were found. The mucous membrane of the pelvis was necrotic and hemorrhagic. The pus contained numerous hard particles

resembling sand. In the right ureter there was an impacted rough stone, 3 cm. from the pelvis. One small stone was found in the opposite ureter 2 cm. from the severed end.

The bladder contained cloudy urine, with much pus, in which many small calculi were found. The mucous membrane contained several hemorrhagic areas with superficial erosions. Aside from cloudy swelling, no lesions of other viscera were found.

The devitalized teeth were markedly discolored, but firm; the cement was in proper place; there was no swelling opposite the roots; turbid fluid was found in the pulp chambers of all four cuspids. The two upper cuspids became infected secondarily. Smears showed gram-negative bacilli, gram-positive diplococci, sometimes in short chains, and staphylococci in varying proportions. Cultures from the infected teeth, from the liver, the substance of the kidney, the blood, the calculi and the pus in the pelvis of the right kidney yielded the streptococcus inoculated, and gram-negative bacilli and staphylococci.

Sections of the right kidney showed marked necrosis of the pelvic mucous membrane, marked infiltration, chiefly by leukocytes, in the medulla immediately surrounding the pelvis, and radiating areas of similar infiltration, in some instances extending along the interlobular tubules well into the cortex. On the basis of these striking results a second series of experiments, in which controls were included, was performed.

The teeth of four dogs were infected with the primary culture in glucose-brain broth from the urine of the patient, and the teeth of four others, with a suspension of a mixture of arthritis strains of streptococci. Four additional dogs were placed under the same conditions without devitalizing or infecting the teeth. One of the four dogs whose teeth were infected with the primary culture from the urine of the patient died of distemper eleven days later. Necropsy revealed extensive bronchopneumonia, cloudy swelling of the viscera, several circumscribed hemorrhages in the mucous membrane of the bladder, and streptococci and staphylococci in the urine, but no focal lesions of the kidneys. There was no evidence of stone formation in the kidneys, nor of periapical infection of the teeth. One dog died of distemper sixteen days after devitalization and infection of the teeth. In this instance necropsy disclosed mucopurulent exudate in the bronchi, extensive bronchopneumonia, coarse, usually adherent, calcareous particles resembling sand in the calices of both kidneys, but no focal lesions, cloudy swelling of the viscera, and slight evidence of periapical infection around the devitalized teeth. The findings in the other two dogs were as follows:

Pathologic Findings.—June 23, 1921, the pulps were removed from the four cuspids of Dog 17 and the canals infected with the culture

from urine obtained from the patient the day previously. The urine and the roentgen-ray examinations of the dog were negative. September 5, the animal appeared to be well. The teeth and cement fillings were firm. A catheterized specimen of the urine contained a small amount of albumin, many leukocytes and calcium oxalate crystals. September 24, the left kidney was removed. Several small, yellow

Fig. 3.—Roentgenogram showing three stones in the right kidney of Dog 17.

Fig. 4.—Kidney of Dog 17 showing stones in the pelvis, and small calcareous deposits in the medulla (× 1).

granules, free and adherent, resembling sand, were found in the calices. The medulla and cortex were free from gross changes, but microscopically numerous small areas of round cell infiltration were found in the cortex, and in the medulla one large area of focal necrosis with marked connective tissue formation in the center, surrounded by round-cell infiltration, and several small linear streaks of lime deposit, with

little surrounding infiltration. A few diplococci were found in the areas of cellular infiltration. The wound healed without suppuration, but the dog soon began to lose weight and much hair, and died October 20.

A roentgenogram made the day of its death contained three distinct shadows of stones in the right kidney (Fig. 3). The kidney appeared to be normal on the surface. The capsule stripped readily. The cortex, aside from cloudy swelling, was normal. The medulla was hyperemic, and in it were numerous small calcareous deposits in the form of small yellowish-white linear streaks and dots, which became larger in the region of the pelvis (Fig. 4). In the pelvis were three hard, yellowish, rough stones, varying in size from 2 by 3 mm. to 3 by 6 mm. The mucous membrane of the pelvis was hyperemic, but otherwise appeared to be normal. The right ureter contained a small, hard, readily dislodged stone, 2 cm. from the kidney. The left ureter

Fig. 5.—Roentgenogram of upper jaw of Dog 17. Note the sharply circumscribed area of rarefaction over the cuspid.

was normal, as was also the mucous membrane of the bladder. In the bladder were numerous small, loose calculi, varying in size from grains of sand to 2 mm. in diameter.

The urine was acid in reaction, and turbid, and the sediment contained a large number of desquamated epithelial cells, a few leukocytes and erythrocytes, and a trace of albumin. In staining smears of the sediment, a moderate number of gram-positive diplococci and an occasional coccus resembling a staphylococcus, but no bacilli, were found. There were no lesions in the other viscera.

The devitalized teeth were markedly discolored, but firm, and the cement was in the proper place. There was rarefaction of the bone opposite each of the devitalized teeth. Over the left upper incisor was a sharply circumscribed area of firm connective tissue capping the root apex (Fig. 5). The rarefied area around the root of the right upper cuspid was large, and capsulation had not occurred; it was filled with

a soft, moist and edematous, partially organizing material. The pulp chambers of all the devitalized teeth contained chocolate colored fluid, in which large numbers of gram-positive diplococci, many in short chains, and small gram-negative bacilli were found.

Shake cultures in blood-agar of the material from the rarefied area around the right upper cuspid contained large numbers of hemolytic

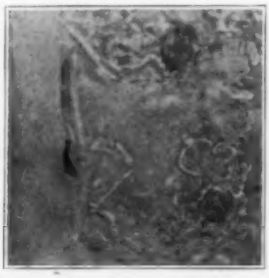

Fig. 6.—Short chain of streptococcus adjacent to an area of crystallization in a collecting tubule in the medulla of the kidney of Dog 17. Gram (× 1,000.)

colonies of gram-negative bacilli and green-producing streptococci, and colonies of staphylococci. Blood-agar plate cultures from the medulla of the kidney, from one washed and crushed stone, and from the sediment of the urine, did not yield growth, whereas glucose-brain broth cultures of the kidney yielded a pure culture of the diplostreptococcus,

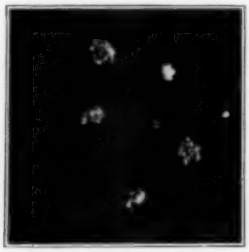

Fig. 7.—Rough, angular calculi from the pelvis of the left kidney of Dog 18. (× 3.)

and of the stone, streptococci and staphylococci. Cultures from the canal of the left lower cuspid yielded the streptococcus and staphylococcus.

Microscopic examination of sections of the right kidney revealed numerous sharply circumscribed areas in the medulla in which crystallization and precipitation of salts were found. These areas varied

greatly in size, some containing only a few well defined crystals, while others were made up of large aggregations of crystalline and amorphous material. In all of the latter, cellular infiltration was slight, and in some, particularly in the areas showing only a few crystals, it was possible to demonstrate diplococci, and at times streptococci in the tissues immediately adjacent to the areas of crystallization (Fig. 6).

June 23, 1921, the four cuspids in Dog 18 were devitalized and the pulp chambers infected with dense suspension of the primary culture of the urine. Blood-agar plates of the suspension inoculated yielded almost pure growth of green-producing streptococcus and a few staphylococcus colonies. Before the inoculation the urine was normal and roentgenograms of the kidney region were negative.

September 24, the dog appeared to be well, and the left kidney was

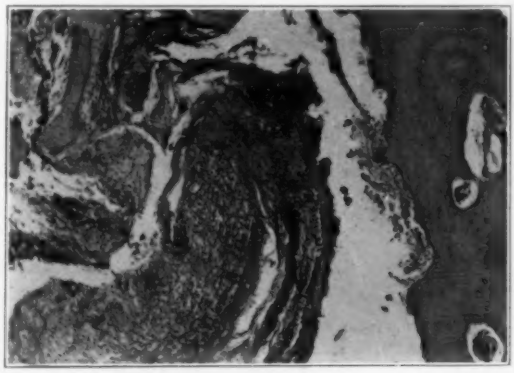

Fig. 8.—Granuloma over the apex of right upper cuspid of Dog 18. Note the irregular cellular infiltration and the invasion of the bony structure. Hematoxylin and eosin (×70.)

removed. Many small, loosely adherent, irregular calcareous particles were found in the calices (Fig. 7). Cultures from this kidney were negative. Microscopic examination of sections revealed one rather large area of focal necrosis, with marked leukocytic and round-cell infiltration low in the medulla, and a few smaller areas of interstitial infiltration. A few diplococci were found in the area of focal necrosis.

Recovery following the operation was prompt, and the wound healed without suppuration. The animal appeared well October 4, but a catheterized specimen of urine contained albumin, a few leukocytes and many calcium oxalate crystals. October 25, emaciation was marked. The animal was chloroformed.

A roentgenogram of the kidney revealed two small, round shadows. The capsule stripped readily. In splitting open the kidney a grating

of the knife edge was noted. The cortex was normal. The medulla contained whitish linear streaks near the pelvis; some of these were calcareous, and in one, projecting into the pelvis, a calculus measuring 3 mm. in diameter was found. In the pelvis were two rather large stones, and in the calices, six smaller ragged ones; the larger stones were free, the smaller ones adherent to the mucous membrane. The ureters and bladder were free from stones and lesions. No lesions were found in the other viscera.

The left lower cuspid had sloughed away, the alveolar socket was filled with pus, and a subcutaneous fistula had formed. Rarefaction was found in the periapical region of the remaining cuspids, and the areas were filled with dense connective tissue (Fig. 8). Sections of

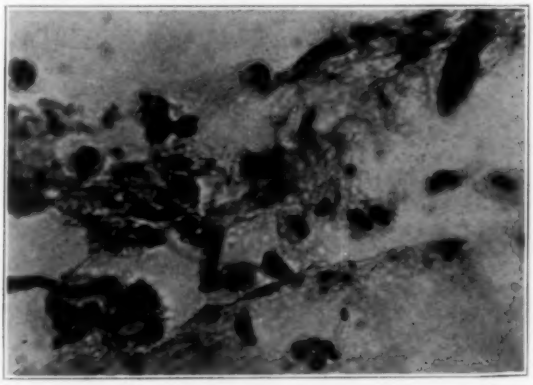

Fig. 9.—Diplococci adjacent to bone in granuloma shown in Figure 8. Gram-Weigert (× 1,000.)

one of these areas revealed marked leukocytic infiltration, varying greatly in intensity, and invasion and absorption of the bony structure. Diplococci and streptococci were found in the areas of cellular infiltration, especially where the bone was eroded (Fig. 9). The pulp chambers were of moderate size and contained thick, chocolate colored pus, in which large numbers of gram-positive diplococci, often in short chains, were found. Cultures from the pus in two of the teeth, and from one of three washed and crushed stones, yielded pure growths of the streptococcus. These cultures were injected intravenously into three rabbits each. All the animals were well at the end of forty-eight hours, when they were anesthetized. Two in each group had mild lesions in the medulla of the kidney, and one in each had lesions of the bladder. Two also had a few lesions in the muscles, but no lesions were found elsewhere. The fermentative power of the strepto-

coccus from the right upper cuspid was identical to that of the streptococcus from the kidney of Dog 17 and from the urine of the patient. Glucose, maltose, saccharose and raffinose were fermented, while manite, salicin and inulin were not. The streptococcus from the stone fermented glucose, maltose and salicin, but not saccharose, raffinose, manite or inulin.

Sections of the right kidney revealed a number of small sharply circumscribed areas of interstitial infiltration with leukocytes and round cells, and areas of varying size containing crystals resembling calcium oxalate, in which leukocytic and round-cell infiltration were absent or slight. These were largest in the papillae just beneath the mucous membrane of the pelvis (Fig. 10), became progressively smaller up

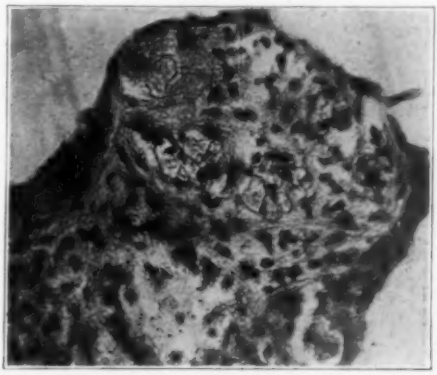

Fig. 10.—Area of crystallization, and slight infiltration in medulla adjacent to the pelvis in the right kidney of Dog 18. Hematoxylin and eosin (+ 220).

along the tubules in the medulla, and were absent in the cortex. The demonstration of organisms in the larger areas was not accomplished, while adjacent to the smaller areas, especially those that still contained a few infiltrating cells and homogeneous exudate, gram-staining diplococci, sometimes in short chains, were found (Fig. 11).

The mixture of streptococci from arthritis inoculated into the teeth of four of the control dogs represented four strains isolated from four cases of subacute arthritis. They were cultivated from the joints of rabbits that developed arthritis following intravenous injection of the primary culture in glucose-brain broth from infected teeth or tonsils. Each strain had been kept in dense suspension in glycerin and concentrated salt solution for from one month to six weeks. Plating on blood-agar of the suspension inoculated yielded a large number of colonies of green-producing streptococci.

One of these dogs died on the sixty-second day, after marked loss in weight. No gross lesions of the joints, muscles, or kidneys were found. One died of distemper five days after devitalization and infection of the teeth, and one in fourteen days. No stones were found, nor was any arthritis noted. One dog gained in weight. The left kidney was removed ninety-nine days after the teeth were infected, and the animal was chloroformed on the one hundred and twentieth day. Both kidneys and the joints were normal.

A medium sized granuloma was found capping each of the four devitalized teeth. The pulp chambers of three contained small amounts of chocolate colored pus. From these the green-producing streptococci, a few staphylococci, and gram-negative bacilli were isolated. In the

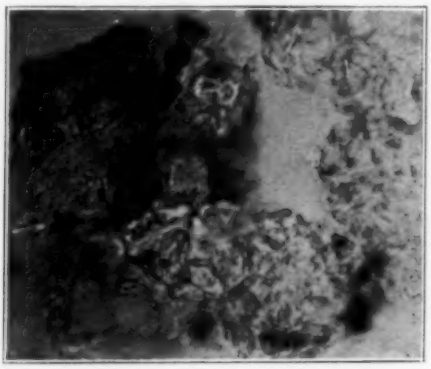

Fig. 11.—Diplococci and leukocytes adjacent to an area (lower portion of field) showing crystallization in the medulla. Gram-Weigert (×1,000).

other tooth the pulp chamber was dry, and cultures yielded the streptococcus in pure growth. This was injected intravenously into two rabbits of the same weight. Both animals were disinclined to hop, and were anesthetized forty-eight hours after injection. One rabbit had suppurative arthritis of both knee joints and one shoulder joint; in the other rabbit there was slighter turbidity of the knee joint fluid, and marked hemorrhages and edema of the muscles around the knee joints near the tendinous ends.

A pure culture of the streptococcus was isolated from the blood and joints of each rabbit. Four additional rabbits were injected, two each with the cultures from the blood of these rabbits, one representing a pure arthritis strain, the other a myositis-arthritis strain. All four rabbits survived, sat quietly, and were disinclined to hop. They were anesthetized forty-eight hours after injection. The two injected with

the pure arthritis strain developed suppurative arthritis of both knee joints, shoulder and ankle joints, one without lesions of muscles, the other with only a few small hemorrhages in the tendinous end of the muscles on the inner side of the left knee joint. The two injected with the myositis-arthritis strain developed marked periarticular hemorrhages of ligaments and adjacent muscles, and relatively slight turbidity of the joint fluids, the picture of a periarthritis. Cultures from joint fluids in all again yielded the streptococcus in pure form. No lesions were found in the kidneys of the six rabbits injected.

Of the four additional control dogs, one died of distemper fourteen days after being placed under conditions similar to those of the dogs whose teeth were devitalized and infected. The left kidney of each of the other three dogs was removed after ninety-nine, ninety-nine, and 140 days, and the dogs were killed after 120, 120, and 118 days, respectively. The kidney and urinary bladder in all of these were free from stones and were otherwise normal. Cultures in glucose-brain broth from the apical ends and pulps of two vital teeth, and from the kidney structure of two of the dogs proved negative. Sections of the right kidney of each of the three dogs were examined and all were free from lesions. The urine remained normal, roentgenograms remained negative, and the animals gained in weight and were active and playful throughout the experiment.

In the third series of experiments, begun March 8, 1922, there were four dogs whose teeth were infected with the primary culture of the streptococcus from the urine of this patient during a quiescent interval, two dogs whose teeth were merely devitalized, and four dogs whose teeth were devitalized and infected with an avirulent strain of *Staphylococcus albus*. All of the ten dogs remained well and were anesthetized in from three to five months. Three of the dogs in the first group revealed small calculi in the medulla and calices at necropsy, and microscopic deposits of lime salts and areas of cellular infiltration in the medulla. The fourth dog in this group, and the six control dogs were free from calculi and other lesions. The streptococcus isolated from the medulla of the kidneys of the three dogs that had lesions was injected intravenously into ten rabbits. Seven developed lesions in the medulla of the kidneys; three were free from lesions.

The fourth series of experiments was conducted on two dogs whose teeth were inoculated with the streptococcus from the tooth extracted October 21, 1921, and on two control dogs inoculated with the streptococcus from the tonsils of a patient with vague urinary symptoms. The first two dogs developed gross and microscopic calculi in the medulla or calices of the kidneys, and areas of active infiltration in the medulla. The control dogs were free from calculi and other lesions.

RESULTS IN THE NINE CASES STUDIED

Owing to the numerous instances of beneficial effects in other diseases from the removal of foci of infection and to the results obtained in our first case, the tonsils were removed and infected teeth extracted in the other patients studied. The extracted teeth and extirpated tonsils afforded us opportunity to obtain proper cultures for experimental studies.

All of the patients studied were men. Their ages ranged from 33 to 60 years. All were suffering from nephrolithiasis, had had typical renal attacks of from three to twenty years' duration, and the interval from the last attack to the time of our study ranged from two weeks to nine months. A history of acute infection which appeared to be a factor in the genesis of the urinary symptoms was obtained from three of the patients. Cultures were made from the urine of five of the patients. From three of these urines streptococci, usually with staphylococci and *Bacillus coli*, were isolated. Foci of infection were found in the teeth or tonsils of all. The number of pulpless teeth showing periapical infection varied from one to seven in each patient. Most of the infected teeth had been rendered pulpless many years prior to our study. The teeth of dogs were infected with cultures from teeth, tonsils, and urine of one patient, from teeth and tonsils of two, from infected teeth only of four, and from tonsils only of two.

Twenty of the thirty-four dogs used in the experiments developed calculi and other lesions in the urinary tract, readily visible at necropsy. Twenty-six (75 per cent.) revealed microscopic calculi in the medulla of the kidney, and twenty had localized areas of active cellular infiltration in the medulla. Thirty dogs (87 per cent.) revealed either calculi or localized lesions in the medulla, or both. Streptococci or diplococci were demonstrated in, or adjacent to, lesions in the kidney in sixteen dogs, all of which showed active focal lesions on microscopic examination. Positive results were obtained in eight of the nine cases. In the negative case the teeth of only one dog were infected.

The duration of the experiments yielding positive results was one month in two of the dogs, from two to three months in eight, from three to six months in twelve, from seven to eight months in six, and ten months in two. The duration of the four negative experiments was only eleven, fifteen, thirty and forty-five days, respectively, because of death from distemper.

The number of dogs whose teeth were infected with cultures from the patients varied from one to twelve in each case. In two cases only one dog was used, in three cases, two dogs, in two cases, four dogs, in one case, six dogs, and in one case twelve dogs were used. The teeth of eighteen dogs were inoculated with cultures obtained from infected teeth, six with cultures from tonsils, and ten with cultures

from the urine. Twenty of the dogs were anesthetized and fourteen died of intercurrent infection or as the result of the induced focal infection.

In nearly all instances cultures from the pus found in the pulp chambers, which showed many streptococci and leukocytes in smears, yielded streptococci resembling those inoculated, usually with small gram-negative bacilli. This was true alike of the three cuspids infected at the time of the operation and the one cuspid in each dog which was merely devitalized and sealed in a sterile manner.

The localizing power in rabbits of the streptococcus from the teeth was tested at the end of each experiment in sixteen of the thirty-four dogs.

Forty-two rabbits were injected. Focal lesions were found in the medulla of the kidneys in twenty-one. Lesions in other organs were rarely obtained. Five had lesions in the periosteum opposite the roots of the incisors, three in skeletal muscles, three in the myocardium, two in joints, one in the gallbladder, and one had ulcer of the stomach.

Of the sixteen dogs from whose teeth cultures were made and injected intravenously into rabbits, ten, representing four cases, showed microscopic evidence of active focal lesions in the medulla of the kidney. Of the twenty-eight rabbits injected, twenty-one developed focal lesions in the medulla, and seven showed no changes. The remaining six dogs, representing four cases, showed no microscopic evidence of active lesions in the kidney, and all of the fourteen rabbits injected remained free from lesions in the kidneys.

Streptococci resembling those inoculated into the teeth were isolated from the urine at necropsy in fifteen of the twenty-three dogs in which cultures were made, from the kidney in seven of twenty-seven dogs, and from renal calculi in three of six dogs. The positive cultures from the urinary tract were all obtained from dogs whose kidneys showed active lesions on microscopic examination. The primary cultures of the streptococcus from the urine, kidney, or calculi of five dogs, representing three cases, were injected intravenously into sixteen rabbits. Of these eleven revealed localized lesions in the medulla of the kidneys, while five remained free from lesions.

The staphylococcus which was isolated in small numbers from the urine of our first patient, and from several stones and some of the teeth of the dogs always failed to localize in the kidney on intravenous injection into rabbits and was not demonstrable in the areas showing beginning stone formation.

The strains of streptococci from the different cases with which positive results were obtained were much alike. All produced small, rather dry, nonadherent green colonies on blood-agar plates; all were of a low grade of virulency, and produced marked acidity in glucose broth.

The lesions in the kidneys of rabbits following intravenous injection were similar to the active lesions in the dogs. They were not numerous, and not necrotic, and were nearly always small and limited to the medulla. Those following the injection of the urine cultures were the more pronounced. By placing thin pieces of fresh tissues immediately into solutions of neutral red, and by treating sections of the fixed tissues with nitrate of silver, it was found that deposition of lime salts occurred in lesions in the kidney, and in a few instances in lesions of the myocardium, as early as forty-eight hours after injection. Microscopic examination of the kidneys of the dogs showed three main types of lesions, sharply circumscribed areas of leukocytic infiltration between the collecting tubules, more diffuse areas of round-cell infiltration (Fig. 12), and deposits of oxalate crystals (Fig. 10)

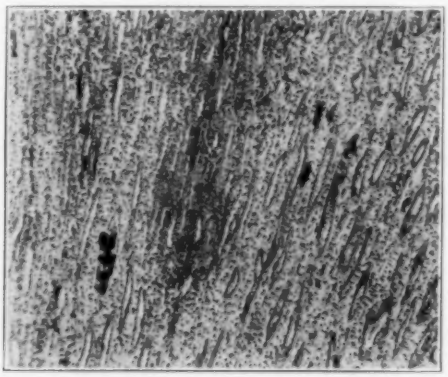

Fig. 12.—Section of the medulla of the kidney of a dog whose teeth were devitalized and infected five months previously. Note the four areas of calcium deposit and the linear areas of cellular infiltration. Hematoxylin and eosin (×50).

or amorphous lime salts, with little or no surrounding cellular infiltration (Fig. 12). The number of bacteria in the lesions was always small (Figs. 6, 11, 13, and 15); long search was often necessary for their demonstration. They were never found in normal tissue remote from lesions, nor in the kidneys of ten dogs in which localized areas of cellular infiltration were absent and in which the areas of lime deposits had healed. Sections of other viscera in some of the dogs that had stones were uniformly free from changes.

CONTROL EXPERIMENTS

Besides the twelve control dogs in our first case, we have studied the results in twenty-three additional dogs whose teeth were infected

with cultures of streptococci or staphylococci from sources other than nephrolithiasis, and which were kept under the same conditions with regard to diet, and so forth, as those inoculated with the nephrolithiasis strains. Areas of rarefaction around the apices of the infected teeth from which the inoculated organisms were recovered were found in most instances. Five (14 per cent.) of the thirty-five animals revealed calculi and lesions of the medulla of the kidneys. The calculi were small and situated chiefly in the medulla or calices. Sections revealed small localized areas of infiltration and areas of lime deposits in the medulla, with little or no cellular infiltration, in which diplococci were demonstrated. Since the organisms inoculated into the teeth of these dogs had no affinity for the kidney, it was thought that the small calculi found in this series were of spontaneous origin, and that calculi

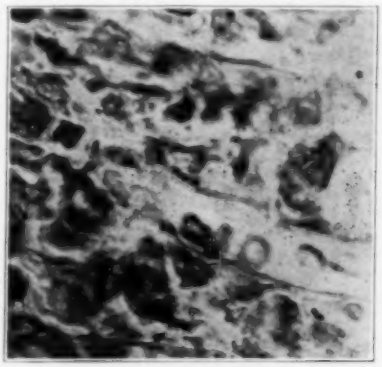

Fig. 13.—Diplococci in the area of cellular infiltration shown in Figure 12. Gram (× 1,000).

in dogs may also be due to infection. Through the kindness of Dr. Hardenburgh we have had opportunity to test this hypothesis experimentally and are able to include, as a further check on our experiments, the results of his routine examination of dogs kept under similar conditions during the course of our study. Of 433 dogs examined, fifty (11 per cent.) had urinary calculi. In most of these the calculi were small, flat and loosely adherent to the mucous membrane of the calices. None was as large as those illustrated in Figures 2 and 4. The gums around the teeth of many showed varying degrees of infection. Urinary calculi were not found at necropsies performed by one of us on 581 dogs over a period of ten years. According to Hutyra and Marek,[4]

4. Hutyra, F., and Marek, J.: Special Pathology and Therapeutics of the Diseases of Domestic Animals, London, Baillière, Tindall and Cox, **1**:1149, 1912.

calculi were found in only twelve (0.38 per cent.) of 3,301 dogs examined at the Dresden Pathological Institute. The experience of others indicates a general low incidence of this condition in normal dogs.

The experiments to determine the etiology of spontaneous calculi in dogs consisted of culturing the medulla of the kidneys containing calculi, and the washed and crushed stones, of testing the localizing power of freshly isolated cultures on intravenous injection in rabbits, and of inoculating the teeth of dogs with the organisms isolated from the induced lesions in the kidneys of rabbits. Pure cultures of streptococci were isolated from the medulla of the kidney or from the stones of each of five dogs showing spontaneous calculi. One of these produced hemolytic colonies on blood-agar plates, one indifferent colonies, and three green colonies. The indifferent strain was injected into

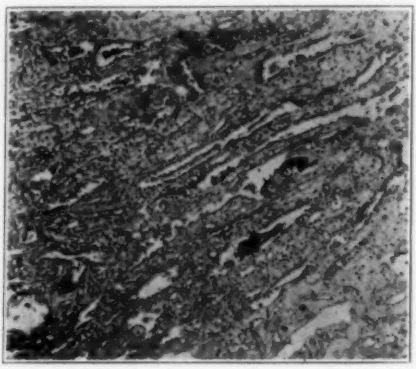

Fig. 14.—Section of the papilla of a dog that developed spontaneous calculi. Note the areas of lime deposit, and slight cellular infiltration. Hematoxylin and eosin (× 50).

four rabbits, and one of the green-producing strains into one rabbit. All remained well and free from lesions, and the strains were lost. One of the remaining green-producing strains produced lesions of the medulla of the kidneys in two rabbits injected. The primary culture of the third green-producing strain isolated from the stone of one of these dogs produced lesions in the medulla in three of four rabbits, and one of two dogs injected intravenously. The strain from one of the positive rabbits produced lesions in the medulla of the kidneys of two rabbits, and the strain from the positive dog, in the one rabbit injected. Cultures from the kidneys showing lesions were positive in every instance, and negative where no lesions were found. Cultures from the blood were negative in all. The strain isolated from the kidney of this dog, culturally and morphologically identical to the one isolated from the stones, was without effect in four rabbits

injected. No lesions were found, and cultures from the kidneys and blood were sterile.

The hemolytic streptococcus in the third subculture was injected intravenously into two rabbits. Both developed lesions in the medulla of the kidneys, and cultures of the urine and kidneys yielded pure growths of the streptococcus injected. This strain produced lesions in all of three rabbits injected. The culture from the kidney of one of these was then injected into two rabbits. Both died, and marked lesions of the kidneys were found at necropsy. The culture from the kidney of one of these in turn was inoculated into the teeth of two dogs. They lost weight, but seemed well six months later, when they were anesthetized. Both had developed calculi in each kidney, demonstrable by the roentgen ray. Sections revealed localized areas of lime deposits and circumscribed areas of relatively slight round-cell infiltra-

Fig. 15.—Chain of two diplococci immediately adjacent to the largest area of calcium deposit shown in Figure 14. Gram (× 1,000).

tion in the medulla (Fig. 14), in which diplococci were demonstrable (Fig. 15). The streptococcus inoculated into the teeth was isolated from the teeth and from the kidney stones and urine in pure culture at the end of the experiments. The cultures from the stones and kidneys produced lesions in the medulla of the kidney in all of seven rabbits injected intravenously, from which the streptococcus was isolated in pure culture in every instance. The blood was sterile in six and contained the organism in one.

Four control dogs placed under identical conditions during the course of the experiment were found free from calculi.

SUMMARY AND DISCUSSION

The streptococcus inoculated into the pulp canals was isolated from the infected material in the root canals or the periapical tissues of the pulpless teeth at the end of each experiment. This was true alike of

the three cuspids which were devitalized and infected at the beginning of the experiment and of the cuspid which was devitalized but not infected. In some instances secondary infection by a small gram-negative bacillus, and more rarely by a staphylococcus, had occurred. The streptococci in the teeth in which secondary infection had not occurred were especially numerous at the periphery of well formed granulomas and where the bone was being absorbed. The findings around the teeth were similar to those following the devitalization of teeth in persons, as practiced in dentistry: the infected teeth became discolored, but remained firmly in place in the alveolar sockets; the infection caused rarefaction and absorption of bone in the periapical region without swelling, pain, or tenderness, and the cellular infiltration and distribution of the bacteria of well formed granulomas were also similar.[5] The experimentally produced chronic foci, aside from being the source of the streptococcus which tended to localize electively in the urinary tract, appeared to have a general deleterious effect. Some of the dogs lost markedly in weight and became more susceptible to intercurrent infection. This was particularly true in those in which unusually large areas of infection around the teeth had developed and in which the renal calculi were large. This finding supports the interpretation by Osborne and Mendel[6] of the infectious origin of urinary calculi observed in rats (eighty-one of 857) fed on a diet deficient in fat soluble vitamins.

It is not clear why the four dogs infected with the arthritis streptococci failed to develop arthritis. Active infection around the teeth was found in all. The streptococcus from the pulp chamber in one of the dogs inoculated four months previously had retained its affinity for the joints of rabbits on intravenous injection. It would seem, therefore, that the joints of these dogs were not affected because of high resistance of these structures to invasion by this organism during the relatively short duration of the experiment.

Calculi or lesions of the medulla were produced in 87 per cent. of the dogs whose teeth were infected with streptococci from the urine, infected teeth, and tonsils of nine patients with typical nephrolithiasis. The duration of the experiment on the dogs in which the findings were negative was too short for stones to form. This is in sharp contrast to the findings in an equal number of dogs whose teeth were infected with strains from other sources, and to those of a larger series kept under the same conditions but in which the teeth were not infected.

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5. Rosenow, E. C.: Studies on Elective Localization. Focal Infection with Special Reference to Oral Sepsis, J. Dent. Res. **1**:205, 1919.

6. Osborne, T. B.; Mendel, L. B., and Ferry, E. L.: The Incidence of Phosphatic Urinary Calculi in Rats Fed on Experimental Rations, J. A. M. A. **69**:32 (July 7) 1917.

The experimentally produced calculi were similar in physical properties and chemical composition to those found in nephrolithiasis in man. The number and size of the stones were often proportional to the duration of the experiment. The other findings in the urinary tract were also similar to those occurring in patients with this disease.

If albumin, pus and blood were present in the urine, there were only small amounts; and the lesions in the medulla of the kidneys were relatively slight unless ureteral obstruction from an impacted calculus occurred, when marked ascending infection developed just as it commonly does in patients with partial obstruction of the ureter, and as produced experimentally in dogs by Keith and Snowden.[7]

The streptococcus inoculated into the teeth of dogs was isolated from the kidneys, from some of the stones, and from the teeth at the end of the experiments, and its elective affinity for the urinary tract in rabbits was demonstrated on intravenous injection. The streptococcus from the teeth of dogs that showed active lesions in the kidneys had retained specific affinity for the kidneys of rabbits, while those from the dogs that showed no lesions or only healed lesions had lost this peculiar localizing power. The organism was found in the lesions in the substance of the kidney where crystallization and stone formation were beginning.

The results of our experiments and the clinical study by Keyser and Braasch,[8] and others [9] indicate that the factor of focal and other infections should be given thorough consideration in the management of cases of nephrolithiasis. And may not a stone-forming infection account in part for the unusual prevalence of this condition in certain localities? The demonstration of the presence of the microorganisms precisely where precipitation and crystallization begin suggests strongly that the mechanism of the production of stone is largely a local process and that the reactions incited produce the physicochemical conditions necessary, such as the nucleus and organic framework, for the formation of calculi. The common occurrence, however, of unusually large numbers of calcium oxalate and other crystals in the urine and in the medulla of the kidneys of the dogs that developed calculi, and the loss in weight, suggest that more general effects of infection may also play a part.

The conclusion that primary urinary calculi are often due to streptococci which have elective affinity for the urinary tract and, it would seem, specific power to incite the conditions necessary for their formation seems justified.

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A STUDY OF MACROPHAGES IN THE HUMAN BLOOD WITH SPECIAL REFERENCE TO THEIR PRESENCE IN TWO CASES OF SUBACUTE BACTERIAL ENDOCARDITIS *

JOHN J. SAMPSON, M.D., WILLIAM J. KERR, M.D.
AND
MIRIAM E. SIMPSON, PH.D.
SAN FRANCISCO

It is the purpose of this paper to present two cases of malignant endocarditis associated with *Streptococcus viridans* septicemia, showing some unusual cells termed macrophages in the peripheral blood. The morphologic and functional characteristics of these cells corresponded closely with cells produced experimentally in rabbits by one of us.[1] It is because of this similarity that we hope to offer some suggestions which may help to clarify the nature and relationship of these and other mononuclear cells found in the blood.

The cells which we term macrophages (Metchinkoff, H. M. Evans) because one of their striking characteristics is a marked power of phagocytosis, have been synonomously termed pyrrhol cells (Goldman), adventitia cells (Marchand), histogenous macrophages (F. A. Evans), histiocytes (Aschoff, Kiyono), resting wandering or polyblast cells (Maximow), rhagiocrine cells (Renaut), endothelial leukocytes (Mallory), and clasmatocytes (Ranvier), although some of the above terms included in their scope additional mononuclear cells to those described herein.

A wide range of pathologic conditions seem to stimulate the production and release of these cells into the peripheral blood, although they have never been found there in normal humans or other mammals. Thus mononuclear phagocytic cells have been described in active endocarditis by Schilling,[2] Leede,[3] Hynek,[4] and Netousek[5] (the latter also observing them in experimental septicemias); in typhoid fever by

* From the Departments of Medicine and Anatomy of the University of California Medical School.

1. Simpson, M. E.: The Experimental Production of Macrophages in the Circulating Blood, J. M. Research **43**:77, 1922.

2. Schilling, V.: Ueber hachgradige Monozytosen mit Makrophagen bei Endocarditis Ulcerosa . . . . , etc., Ztschr. f. klin. Med. **88**:377, 1919

3. Leede, W.: Ein Fall von Endocarditis ulcerosa mit krankhaft entarten Lymphozyten im Blut, Mitt. a. d. Hamburg. Staatsanstalt. **12**:411, 1911. (Reviewed in Folia hematol. **13**:53, 1912.)

4. Hynek, K.: Zur Monozytenfrage, Folia hematol. (Archiv.) **13**:345-383, 1912.

5. Netousek, M.: Uber Endothelien und ihre Beziehung zu den Monozyten, Folia hematol. **19**:1-11, 1914.

Eichorst,[6] Mallory,[7] McCallum,[8] and Netausek [5] (in typhoid vaccination by Miller and Pepper [9]); in malaria by Pappenheim,[10] Schilling [2] and Bushnell;[11] in tuberculosis with mild nephritis, and mesenteric tuberculosis with secondary sepsis by Schilling;[2] in cholera by Netausek;[12] in a chronic heart case with intestinal parasites and erysipelas by Van Nuys;[13] and in a chronic heart case in which they were found in localized leukocytosis in the lobes of both ears only, by Bartlett.[14] They were first experimentally produced by Aschoff and Kiyono.[15]

In these cases there is apparently a definite etiologic agent. There may be pointed out in addition a series of cases with obscure cause, in which at least recognized irritating or stimulating material such as toxins, colloids, or particulate matter is not known to be thrown into the blood stream. Such are the cases of monocyte (transitional) leukemias (Schilling,[2] Reschad and Schilling,[16] Jochman and Blühdorn,[17] of Van Jaksch's chlorosis anemia and anemia with splenomegaly (former two cases of Netausek,[5] latter of Fr. Krauss [18]), of "fatal anemia" (Rowley [19]), and possibly of paroxysmal hemoglobinuria (Ehrlich, Eason, Kömmer and Meyer [20]), and of the blood distally to the point at which the chief vein of a limb has been ligated proximally

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13. Van Nuys, F.: An Extraordinary Blood; Presence of Atypical Phagocytic Cells, Boston M. & S. J. **156**:390-391, 1907.

14. Bartlett, W. B.: Localized Leukocytosis Associated with Atypical Phagocytic Cells, Boston M. & S. J. **156**:629-630, 1907.

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16. Reschad, H., and Schilling, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie und ihre Bedentung für die Selbstandigkeit dieser Zellen), München med. Wchnschr. **60**:1981-1984, 1913.

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19. Rowley, Mary W.: A Fatal Anemia with Enormous Numbers of Circulating Phagocytes, J. Exper. M. **10**:78-97, 1908.

20. Ehrlich; Eason; Kommer and Meyer; quoted from Simpson, M. E.: J. M. Research **43**:77-144, 1922.

TABLE 1.—The Blood Findings in the Case of C. P.

Date, 1921	Total White Count	Polymorphonuclear neutrophils, per Cent.	Myelocytes, per Cent.	Eosinophils, per Cent.	Basophils, per Cent.	Lymphocytes, per Cent.	Macrophages, per Cent.	Intermediate Forms, per Cent.	Monocytes, per Cent.	Platelets	Erythrocytes in Millions	Remarks
5/ 5	4,800	....	1	..	..	....	+	..	..	..	3.27	Blood culture, streptococcus viridans in 5 days; sputum culture, streptococcus viridans
5/22	.....	....	..	..	..	....	0					
6/ 4	13,200	....	..	..	..	....	1	..	5	..	3.52	
6/ 5	.....	....	..	..	..	....		30	17			
6/ 6	.....	....	..	..	..	....	0	2	9			
6/ 7	.....	....	..	..	..	....	0	..	9			
6/ 9	.....	66.5	0	0	0	30.5	0	0	4	..	....	Blood culture, streptococcus viridans after 5 days
6/10	.....	....	..	..	..	....	0	1	4	..	....	One hour before transfusion; 15 hours after transfusion
6/11, 10:30 a.m.	.....	....	..	..	..	....		9	5	++	....	Identical result with fixed and vitally stained films
2:30 p.m.	11,000	....	..	..	..	....	..	1?	3	..	....	Twenty-four hours after transfusion
6/12, 2:30 p.m.	.....	....	..	..	..	....	16 complete gradation					
6/14	.....	....	..	..	..	....	29 complete gradation			+	....	Bleeding time, 4 minutes
6/16	.....	44	0	1	0.5	16.5	39 complete gradation			++		
6/17	.....	....	..	..	..	....		9	6	..	....	Fixed film from splenic puncture numerically identical with vitally stained film
		74.5	0	0.5	0	17		8				
							0			..	....	Fixed film from ear
							0	..	½	..	....	Vitally stained film from ear
6/19	.....	....	..	..	..	....	0	..	8			

6/21, 11:00 a.m.	.....	....	..	..	..	....	11 complete gradation	..	....	Four hours before transfusion
3:40 p.m.	.....	....	..	..	..	....	.. 6	..	....	Forty minutes after transfusion
6:40 p.m	.....	....	..	..	..	....	24 complete gradation	..	....	Three hours forty minutes after transfusion
6/22	6,600						48 complete gradation	..	3.65	
6/23, 12 m.	.....	....	..	..	..	....	1			
4:00 p.m.	.....	....	..	..	..	....	.. 5	..	....	Fixed film from basilic vein; bleeding time, 8¼ minutes; coagulation time, 6½ minutes
5:00 p.m	.....	....	..	..	..	....	..			
6/24	6,000	....	..	..	..	....	7.5 to 40% (see Table 3)			
6/25	6,000						1			
6/26	7,000	....	..	..	..	....	6	..	....	Twenty-four hours after transfusion
6/29	.....	....	..	..	..	....	5			
7/ 2	.....	....	..	..	..	....	18			
7/ 5	.....	....	..	..	..	....	12			
7/10	....	66	0	0	0	22	0 0	..	2.43	
7/12	5,200	....	..	..	..	....	1 3			
7/13	....	....	.	..	..	....	1			
7/16	9,600									
7/18, postmortem										
Right heart	.....	....	..	..	..	....	1			
Left heart	.....	....	.	..	..	....				

Bracketed figures include all forms covered by bracket. + Slight excess of platelets. ++ Moderate excess of platelets.

(Netousek,[3] and Evans and Schuleman). The two heart cases mentioned above did not come to necropsy and because of the obscurity of any active lesion, and particularly in the unique case of Bartlett's, they may be included in the latter of these two rough divisions.

REPORT OF CASES

Two cases, C. P. and E. W., will be presented, with the inclusion of all important clinical data except the morphologic blood findings (Tables 1, 2 and 3).

CASE 1.—C. P., male, age 18, stenographer, was seen on the medical service of the University of California Hospital.

Family History.—Essentially negative.

Past History.—Pneumonia at 3 months; pertussus at 18 months; measles and mumps at 5 years. Bitten by rabid dog at 12 years; had Pasteur treatments. No symptoms of rabies developed. Influenza in 1918, at 16 years. Apparently uncomplicated.

Figure 1

Fig. 1.—Macrophage from peripheral blood of C. P., showing phagocytized material. Giemsa. × 1500.

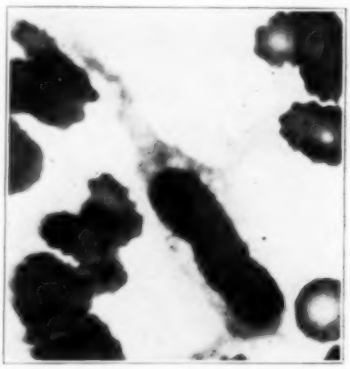

Figure 2

Fig. 2.—Macrophage from peripheral blood of C. P. showing long attenuated process. Giemsa. × 1500.

Present Illness.—Following the attack of pneumonia at the age of 3 months, convalescence was prolonged, and in a few weeks he became severely ill again. Then a valvular heart condition was discovered by the family physician, which was considered to be due to the pneumonia. Since then the patient has lived a restricted cardiac life. Dyspnea, cyanosis and weakness on exertion, with frequent attacks of "bronchitis" supervened. Otherwise he was well until September, 1920, eight months before entry, when he had chills and fever, coming every other day for about two weeks. Oct. 18, 1920, seven months before entry, patient collapsed, became pale and complained of pain in the left hip. Thigh was flexed on abdomen; pain continued for two or three days. Cyanosis of lips and finger tips was noted. He was in bed five weeks but did not regain strength after rising, and on December 20 patient had another chill

and was confined to bed again. Severe bronchitis was diagnosed by the family physician. No dyspnea or cyanosis was complained of during this period. He was an invalid until March, 1921, when he improved slightly and up to entry, May 5, 1921, he felt fairly well. Twelve days before entry, he had another attack of "bronchitis" and vomiting. Purpura appeared two days before entry and there has been a history of previous petechiae. Edema of feet and ankles was noted once prior to entry.

TABLE 2.—Blood Findings in the Case of E. W.

Date	Erythrocytes, Millions	Absolute Leukocyte Count	Polymorphonuclear Neutrophils, per Cent.	Eosinophils, per Cent.	Myelocytes, per Cent.	Lymphocytes, per Cent.	Macrophages, per Cent.	Intermediate Forms	Monocytes, per Cent.	Platelets
1/24.....	2.54	6,800	70	1	0	19	8		2	+
1/25.....	3.27	8,200	83	1	0	9				
1/26.....		11,200	..	..	..	..	3		4	
1/27.....		10,200								
1/29.....		14,600								
1/30.....		11,000								
1/31.....		16,700	..	.	..	..	23, complete gradation			+++
2/ 4.....		24,000								
2/ 9.....		25,000								
2/10.....		12,600								
2/14.....		38,000								
2/15.....		10,000								
2/21.....		94 000	66	1	1	9	23, complete gradation			+++
2/22, 9:00 a.m.		51 000	..	..	..	..	15.5, complete gradation			++
3:00 p.m.		21,000	..	..	..	..	0	..	4	
9:30 p.m.		.....	..	..	..	..	4		4.5	
2/23, 10:30 a.m.		84 000	..	..	..	..	0	0	0.5	
3:15 p.m.		.....	50.5	..	..	4.5	1		44	

Died at 3:30 p.m.

++ Moderate excess of platelets in smear.
+++ Extreme excess of platelets in smear.
Bracketed figures include, in percentage, all forms covered by bracket.

TABLE 3.—Observations on June 24, 1921, in Case of C. P.

Time	Temperature	Pulse	Respiration	Per Cent. Macrophages, Intermediate Types and Monocytes	Remarks
7:30 a.m.	....	....	..	....	Sponge bath
8:00 a.m.	....	....	..	....	Breakfast
8:30 a.m.	37.6	116	24	....	
10:00 a.m.	....	....	..	40	
11:00 a.m.	....	....	..	23.5	
11:30 a.m.	....	....	..	....	Luncheon
12:00 m.	36.8	112	28		
12:30 p.m.	....	....	..	38	
2:00 p.m.	....	....	..	19	
2:30 p.m.	....	..	..	....	Lemonade
3:30 p.m.	....	....	..	7.5	Visitors 2:00-4:30 p.m.
4:00 p.m.	37.0	108	32	....	Stool
4:30 p.m.	....	....	..	....	Supper
5:00 p.m.	....	....	..	15	
6:30 p.m.	.. .	.. .	..	21	
8:00 p.m.	37.4	126	22	....	Sandwich

Physical Examination.—On admission: Punctate purpura on extremities. Malar flush with cyanosis of lips and fingers. Signs of aortic and mitral stenosis and insufficiency, with loud systolic murmur over entire precordia predominating. Liver and spleen enlarged and tender.

May 21: Lungs negative at both bases. Murmurs persisted and a systolic thrill was noted over the precordium most marked at the apex.

Physical condition was approximately the same until June 23, when urine, which had been negative for several weeks, showed an occasional cast, red blood cell, leukocyte and a faint trace of albumin.

July 2, edema of extremities and face was noted with a small amount of ascites. Pustules developed on the skin July 8. Edema and ascites increased. Fundus examination showed some blurring of disc margins. Crepitant râles were present at base of lungs.

July 17, peripheral edema decreased under Karrel diet but edema of lungs and ascites remained unchanged. Respiration and pulse increased and temperature rose from 37 to 38 C. Patient developed decubitus on both scapulae. Heart sounds were fainter. Murmurs constant throughout. Hemorrhagic spots over extremities. Patient died July 18 after short period of delirium.

Laboratory Findings.—Blood Counts: The results of various counts are shown in Tables 1 and 3 and Charts 1 and 3.

Urine: May 5, trace of albumin. Many hyaline and granular casts. Few red blood cells and leukocytes and many epithelial cells.

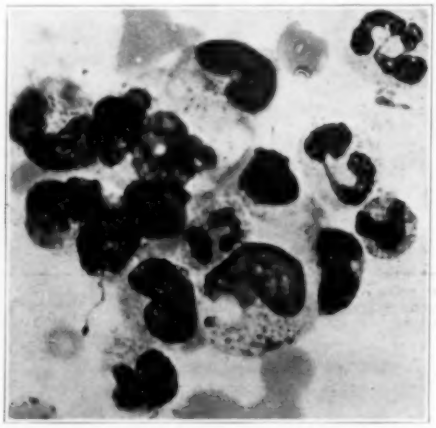

Fig. 3.—Macrophage from peripheral blood of E. W. showing large amount of phagocytized material and vacuolization. Wright's stain. × 1250.

July 23, decrease of number of casts and amount of albumin up to July 23, when shower of red blood cells occurred and increase of leukocytes was noted. Albumin increased to trace on July 6. Casts varied in showers.

Urine Culture: *Streptococcus viridans* on July 6.

Stools: negative.

Blood chemistry, urea nitrogen, 35; nonprotein nitrogen, 64; creatinin, 2.52.

Blood Culture: Showed *Streptococcus viridans* on several occasions. Patient treated by injections of serum of brother who had been given repeated doses of killed cultures of *Streptococcus viridans* vaccine made from patient's organisms.

Clinical Diagnosis.—Subacute bacterial endocarditis, involving aortic and mitral valves. *Streptococcus viridans* septicemia.

CASE 2.—E. W., male, Aged 65, millwright, w observed by one of us on the West Medical Service, Drs. R. C. Cabot and R. I. Lee, of the Massachusetts General Hospital, Boston, January-February 1916.

Family History.—Essentially negative.

Past History.—Jaundice at 4; typhoid at 16; from five to ten years gaseous eructations when a young man. Frequent sore throat up to five years ago. Pleurisy at 62. History of loss of hair (transient) five or six years ago, and of brown papular rash of one week's duration one year ago. Venereal diseases denied. Habits: Alcohol to excess for past six months. Drinks from ten to twenty glasses of ale per day. Weight: Lost 40 pounds in past six months.

Present Illness.—Noted weakness six months before entry after alcoholic excess. One week later severe diarrhea set in, persisted three weeks; stools dark brown, fluid, with mucus but no blood. After two weeks treatment movements decreased and now he has three or four a day, semi-fluid, yellowish with some mucus and no blood. Increased asthenia, lethargy and loss of weight up to present. There is dyspnea without exertion, which is relieved on coughing. Raises daily about 1 ounce of ropey, transparent, blood free sputum. Chills in past two days. No edema.

Physical Examination.—Negative, except that pupils are sluggish to light and distance. Slight dullness and few coarse râles present anteriorly and posteriorly in right chest. Heart: apex impulse in sixth interspace; by percussion outline to left 10.5 cm. from midsternal line in sixth interspace; 3.5 cm. to right in fourth interspace; supracardiac dulness 6.5 cm. at third interspace. Sounds regular, rapid, of fair quality. Second pulmonic sound is equal to the

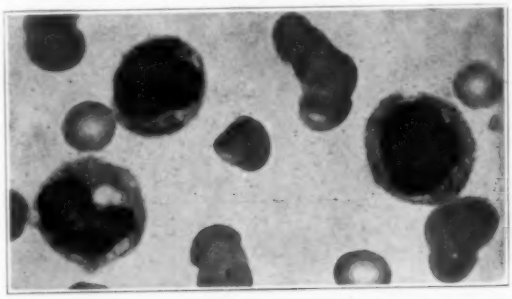

Fig. 4.—Intermediate forms from peripheral blood of E. W. Wright's stain. × 1250.

second aortic. Loud blowing systolic murmur at apex transmitted to axilla. To and fro diastolic and systolic murmur at aortic area. No thrill. Pulses regular, equal, synchronous, of good volume and tension. Liver enlarged, from fifth rib to 4 cm. below costal margin in nipple line. Slight tenderness.

Entered hospital January 24, failing gradually. Temperature from January 24 to 29, from 100 to 103 F., from January 29 to February 21, from 98 to 101 F. February 22, weakness increased; pulse rapid. Temperature increased to 105 F. Respirations rapid and shallow. February 23, death at 3:30 p. m.

Roentgen-ray showed mottling of right upper chest. Conclusion: tuberculosis or syphilis.

Laboratory Findings.—(exclusive of blood). Blood Counts; Table 2 and Chart 2 give data as to blood counts.

Urine: Normal color; acid; specific gravity 1.010 to 1.016; albumin, from slight trace to large trace; no sugar, diacetic acid or acetone; sediment; few granual casts.

Stools: Strong; positive guaiac test on two out of three examinations; once showed stringy clots of fresh blood.

Wassermann: Weakly positive during attack of pneumonia but twice negative since lung sign cleared up.

Renal function (phenolsulphonephthalein): 10 per cent. in two hours.
Blood nitrogen: 38 mg. per 100 c.c. blood.
Blood culture: Negative February 10. Streptococci in both flasks February 22.
Culture from bleb on hand: No growth.
Sputum: January 25. Pneumococcus infection. By mouse inoculation placed in Group IV.
January 27. Pneumococci, few in numbers, continued to be present up to February 6, when the sputum showed almost pure culture of influenza bacilli. February 15, influenza bacilli were present in great numbers.

Clinical Diagnosis.—Subacute bacterial endocarditis of aortic valve; streptococcus septicemia; recent bronchopneumonia.

Necropsy Summary.—Streptococcus septicemia; acute aortic endocarditis with large ulcerating vegetations on valve; soft hyperplastic spleen; moderate arteriosclerosis; slight hypertrophy and dilatation of heart; edema of lungs; chronic pleurisy, obsolete tuberculosis of apices of lungs.

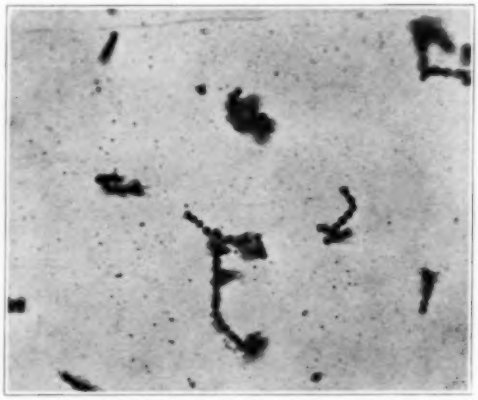

Fig. 5.—Smear from blood culture (E. W.) showing small, short chained streptococci. × 1250.

The striking features in the two cases presented were the similarity of the clinical findings and the presence of showers of unusual, phagocytic, mononuclear cells termed macrophages. The staining methods employed and the morphology of these cells will be discussed in some detail.

STAINING METHODS

In the case of E. W. (Case 2), Wright's stain was used throughout. In the case of C. P. (Case 1), Wright and Giemsa stains, the oxidase and perioxidase stains (diemethyl-paraphenylene-diamine, alpha naphthol and benzidene-hydrogen-peroxide [21] were employed. Cells of C. P.

21. Fischel, R.: Wien. klin. Wchnschr. **23**:1557, 1910; Münch. med. Wchnschr. 57:1203, 1910. (Quoted by Graham, G. S.: J. M. Research **34**:15, 1918, as having priority in use of benzidene.) Graham, G. S.: Benzidine as a Peroxidase Reagent for Blood Smears and Tissue, J. M. Research **34**:15-24, 1918.

Fig. 6.—Large macrophage from peripheral blood of E. W., showing phagocytosis and vacuolization. Wright's stain.

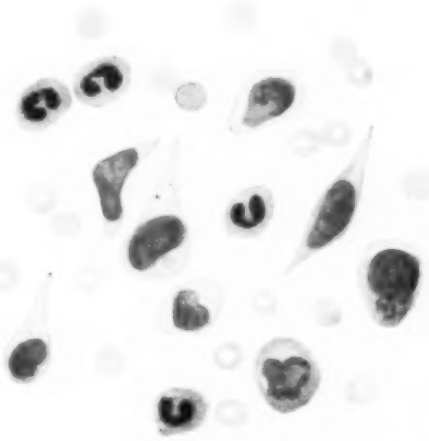

Fig. 7.—Intermediate forms from peripheral blood of E. W. (Wright's stain).

were also studied by a supravital staining method with neutral red and janus green. Smith's stain [22] was used in an attempt to detect the presence of bacteria in the phagocytic cells.

The technic of the supravital staining method used was that of Simpson,[1] developed from Pappenheim [23] and Rosin and Bebergeil.[24] A saturated solution of janus green B in alcohol, in the proportion of three parts of the former to four parts of the latter, are mixed. This mixture is then smeared, in the manner of making a blood smear, on smooth glass slides with perfectly regular surfaces. The film of the dye must be even in distribution and without streaks, and with some experience the optimum thickness will be found. The drop of blood to be examined is placed on a glass coverslip with a smooth, regular surface and inverted on the dye filmed slide. The drop must be of proper size. If the blood film is too thick inadequate staining results and makes proper observation of the cells difficult. The preparations are rimmed with melted paraffin at once. If the directions are followed closely, well stained, living cells should be noted in a layer only one cell deep.

MORPHOLOGY AND STAINING REACTIONS

The size varied from 10 to 80 microns inclusive of the small borderline forms and the cells with long phagocytic processes. The ratio of cell volume to nuclear volume varied from 8:1 to 380:1. The nucleus was either round, oval, indented, polymorphonuclear or multiple (two, rarely three lobes), staining a bright purple with Giemsa, and often definitely vacuolated. The cytoplasm was generally heavily vacuolated and granular, containing phagocytized material of red cells, white cells and other unidentified nuclear material in all stages of disintegration. Pseudopodia and bleblike projections were noted in the living forms but no ameboid motion was observed. Stained with Giemsa the cytoplasm varied from deep blue to colorless, but was always packed with a large number of fine, reddish violet, azurophil granules with occasionally a scattering of coarse ones. With Wright's stain the color of the cytoplasm and nucleus was similar but the finer details of the structure were not necessarily brought out. The oxydase and peroxidase stain of the macrophages as well as the monocytes (Ubergangsformen, transitional and large mononuclear cells

22. Mallory, F. B., and Wright, J. H.: Textbook of Pathological Technique, Philadelphia, W. B. Saunders Company, 1915.

23. Pappenheim, A.: Einige Beimerkungen über Methoden und Ergebnisse sogenannter Vitalfärbungen an den Erythrozyten, Folia hematol. (Central Organ) **9**:90, 1910.

24. Rosin, H., and Bibergeil, E.: Ergebnisse vitaler Blutfärbung, Deutsch. med. Wchnschr. **28**:41-42, 1902.

other than lymphocytes) gave a varying reaction from a heavy deposit to a few fine granules. By supravital staining with neutral red and janus green a heavy segregation apparatus of yellow red granules and numerous mitochondria granules were noted.

A Smith stain showed the presence of what appeared to be chains of streptococci in two out of one hundred macrophages studied. This observation should be taken reservedly because of the large amount of undifferentiated, phagocytized material noted in many of the larger cells.

BORDERLINE FORMS

It has been found by one of us [1] that during showers of macrophages produced experimentally in rabbits, there are forms of mononuclears which cannot be differentiated from the monocytes of the normal blood. These borderline forms have been termed intermediate cells. They occur in complete gradations from the well defined macrophage to the monocyte as determined by size, shape, color reaction and granulation with Giemsa stain; nuclear form, segregation apparatus and mitochondria by supravital staining. All of these criteria have been used in differentiating the cells but as a routine, films were stained with Wright's stain, which does not permit utilization of the segregation apparatus and fine azurophilic granulation as distinguishing points. However, the latter criteria have their chief value in separating the monocyte-macrophage group from the lymphocyte group of mononuclears. The increased size, the bizarre forms, the presence of vacuoles and organized phagocytized material in the former afford sufficient basis to distinguish the macrophages and intermediate forms from the lymphocyte group. The final distinguishing features, as brought out by supravital staining, are more conclusive, as the monocyte-macrophage group show marked fragility which may cause distortion of cells if the coverslip method is used in making film preparations. There is a remote possibility that the intermediate forms may be distorted monocytes, but clinically and experimentally there is evidence against this view, as will be discussed later.

MACROPHAGE FLUCTUATION

One of the striking features of the two cases studied was the marked, rapid fluctuations of the macrophages. This was particularly striking in the case of C. P. (Case 1), in which frequent observations were made over a period of two days. June 23 the percentage of these cells in the total leukocyte count fell from 38 to 1 in four hours, and June 24 it fell from 38 to 19 in an hour and a half and to 7.5 in the succeeding hour and a half (Table I; Chart 2). Other rapid fluctuations were noted. The fluctuations apparently had no relation to temperature, pulse or respiratory changes, time of day, digestion or disturbing

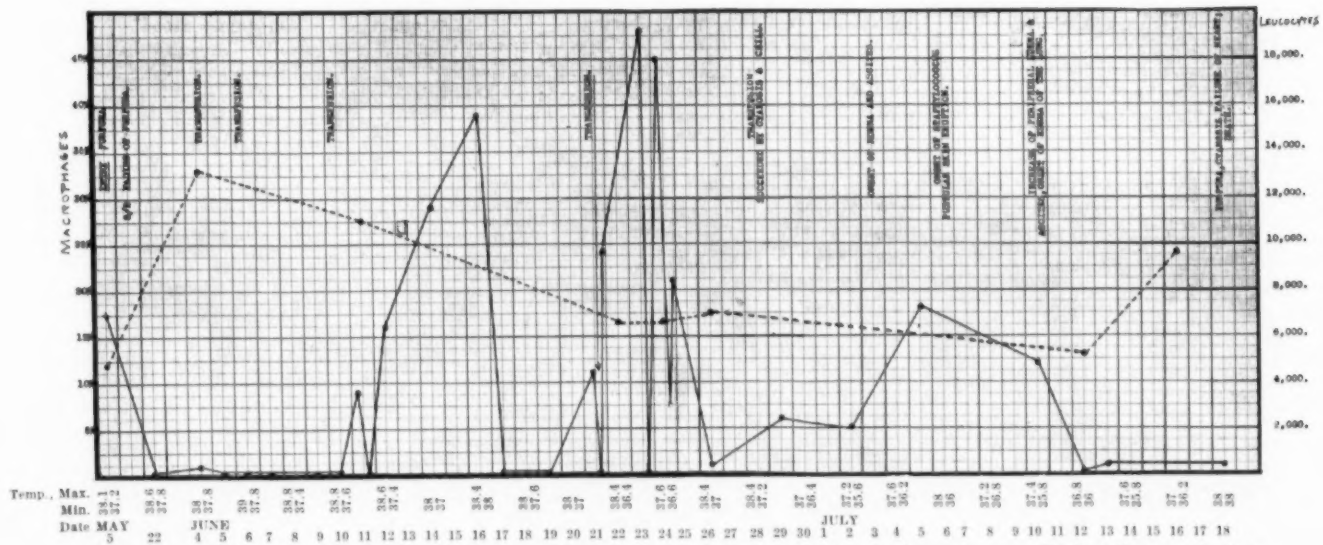

Chart 1.—Macrophage fluctuation in C. P. Solid line = macrophage in absolute leukocyte count. Broken line = absolute leukocyte count.

mental status (Charts 1 and 2). In the case of E. W. (Case 2), the absolute macrophage count paralleled the total leukocyte count except during the terminal leukocytosis. This parallelism was the prevailing condition in the majority of cases presented in the literature. In the case of C. P. the leukocyte count was never high, although the macrophages at times made up from 38 to 48 per cent. of the total leukocytes. The platelets in Case 1 (C. P.) did not grossly increase with the macrophages as was noted in Case 2 (E. W.). In the latter case the high leukocyte count and the high platelet count may have been due to increased bone marrow activity (Tables 1 and 2). The macrophages varied inversely with the bleeding time in the two cases.

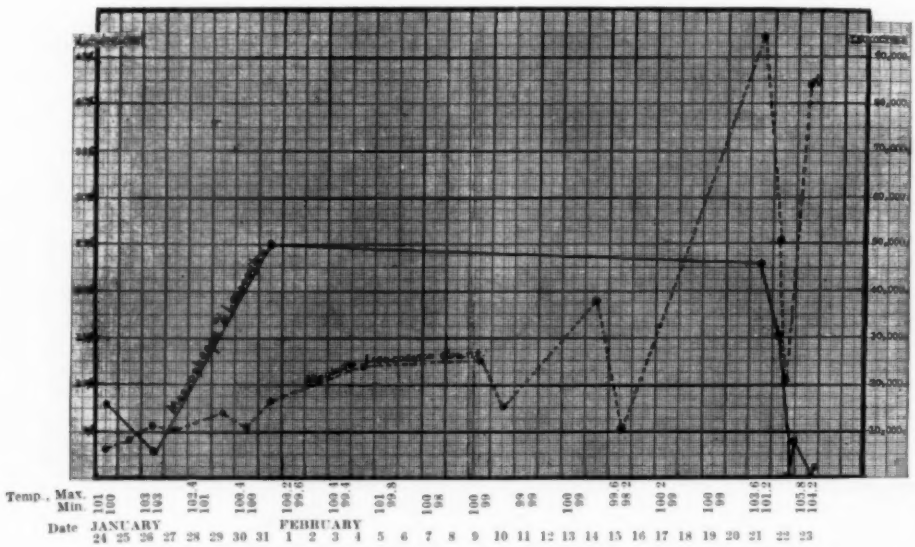

Chart 2.—Macrophage fluctuation in E. W. Solid line = macrophages in absolute leukocyte count. Broken line = temperature in degrees C.

In the case of C. P. (Table 1) transfusions of citrated immunized blood in amounts of from 200 to 250 c.c. were employed as a therapeutic agent.[24] The blood was obtained from a brother who had received subcutaneous injections of a killed culture of streptococcus viridans obtained from the patient's blood. As will be noted from Chart 3, there was an increase in the relative number of macrophages three and fifteen hours after a transfusion. It is suggestive that the introduction of even so closely related a foreign substance as whole citrated blood of the same biologic group (Moss—Group IV), whose content of antibodies as determined by agglutination was 1:50 of that of the

patient, should have stimulated the production of macrophages. This evidence, however, is minimized in view of the rapid daily fluctuations which are known to occur.

In both cases, as will be noted from Tables 1 and 2 and Charts 1 and 2, there was a decrease of macrophages at the time of death which was striking in the case of E. W.

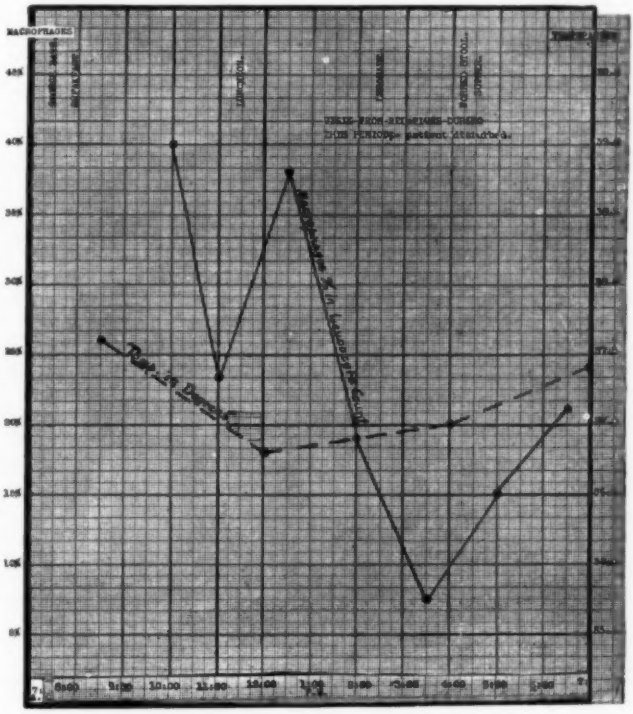

Chart 3.—Daily macrophage fluctuation in C. P.

EXPERIMENTAL STUDIES

Simpson,[1] working with rabbits, showed that repeated injections of certain materials, with a common property of a colloid content,[25]

25. (1) Colloidal dyes: (*a*) 1 per cent. Niagara blue, N. A. C. Co., (*b*) lithium carmine, 5 per cent.; (2) Coarser material held in colloidal state by protective colloids (*a*) red gold with sodium lysalbinate; (*b*) India ink; (*c*) aqua-dag. concentrated, (Acheson Oil Dag Co.); (*d*) lampblack, 5 per cent. in 1 per cent. gelatin; (3) protective colloids of group 2: (*a*) sodium lysalbinate; (*b*) gelatin.

produce an excessive formation of macrophages. These cells were found chiefly in the lesser circulation, making up at times as much as 70 per cent. of the total leukocyte count. In the peripheral blood, however, the macrophages were never more than 6 per cent. and the size was decidedly smaller than that of the cells found in blood from the right heart. Rarely, an extremely large cell was found in the peripheral blood. Examination of the lungs showed the capillaries to be engorged with great numbers of these large cells, suggesting that the low percentage in the peripheral blood and their relatively small size depended on a filtration process in the lungs. There was also noted in the rabbit a rapid fluctuation in the number of these cells in the lesser circulation as well as in the peripheral blood, which suggests some other and possibly a specific mechanism for their removal other than a filter of fixed size.

Observations of the lungs of rabbits during a macrophage shower showed large cells with long attenuated processes extending through the capillaries. It is suggested that these cells have a subsidiary function in the production of platelets to compensate for the low platelet count in purpuric conditions in septicemias. This is in accord with the findings of Bunting,[26] who demonstrated the probability of the nonspecific origin of platelets through the squeezing off of processes of megalokaryocytes caught in the capillaries of the lung in Hodgkin's disease.

The possibility that the peripheral endothelium may be active in the production of macrophages is suggested by the findings in the case of localized leukocytosis described by Bartlett and the monocytosis, distal to a ligatured vein (Evans, Netausek).

The studies of Simpson point to the excessive formation of macrophages from the endothelium of certain organs, chiefly the liver, spleen and lymph nodes. Wright [27] suggests a similar secondary origin for blood platelets.[28]

DISCUSSION

We believe that the macrophage cells described in the two cases of subacute bacterial endocarditis presented were identical with those produced experimentally in rabbits by Simpson. This view is based

26. Bunting, C. H.: Blood Platelets and Macrocytes in Hodgkin's Disease, Bull. Johns Hopkins Hosp. **12**:114-116, 1911.

27. Wright, J. H.: The Histogenesis of the Blood Platelet, Pub. Massachusetts General Hospital **3**:1, 1910; J. Morphology **21**:263-278, 1910.

28. The following references also bear on this subject:

Levison, L. A.: Unsuccessful Result Following Transfusion with Immunized Blood in Infectious Endocarditis, J. Lab. & Clin. M. **6**:191, 1921.

Naegli, O.: Blutkrankheiten und Blutdiagnostik, Ed. 3, Berlin u. Leipzig, Walter de Gayter & Co., 1919.

on their resemblance as regards morphology, staining reactions, phagocytic properties, fluctuations and their disappearance at time of death.

There is fairly conclusive evidence of the identical origin of the macrophages and monocytes from endothelium (Schilling,[27] Evans, Simpson,[1] Mallory [7]). The work of Simpson points to their origin in the liver, spleen and lymph nodes with the discharge of these cells into the lesser circulation in response to certain stimuli. Experimentally, the lung capillaries probably act as filters, allowing only the smaller cells to pass into the peripheral circulation. The proportion of these cells to the total leukocyte count in the peripheral blood is higher than in experimental animals, suggesting also a peripheral origin. This is in accord with the findings of other observers, especially in the localized leukocytosis of Bartlett and the observation of monocytes, peripheral to a ligatured vein (Evans, Netausek [5]).

The stimuli causing the production of macrophages and their release into the blood stream have been studied experimentally by Simpson. It was shown that colloidal dyes, coarser material held in colloidal state by protective colloids, or protective colloids alone, by repeated injection, were capable of calling forth these cells. The common property of these substances was the colloid content. Thus we may assume that in addition to such substances as bacteria, foreign particulate matter, or chemical compounds, which are known to be capable of altering the absolute or relative blood count, the mere change in proportion of certain colloid elements, as the normal blood proteins, may stimulate the production or release of cells into the blood stream. It is suspected that some such alteration of the colloid content in the blood may be the basis for the production of macrophages in these cases. There is apparently no relation clinically between the fluctuations of these cells and those factors which cause definite variations in the leukocyte counts, such as fever, pain, digestion, embolic phenomena or bacterial showers, etc.

Macrophages observed in the peripheral blood in man were generally smaller than in experimental rabbits, while the relative number was increased in the human observations. These findings suggest that the cells liberated into the blood stream clinically are smaller because the mother tissues produce smaller cells in man or that a more protracted stimulus of a long continued infection calls forth smaller cells.

Simpson discusses the possibility that the macrophages may engulf substances of certain limited sizes, and in such conditions as endocarditis these cells may be called out to handle such substances as the other phagocytes are incapable of dealing with.

SUMMARY

1. In two cases of subacute bacterial endocarditis, cells foreign to the normal blood stream were observed. They varied in size from 10 to 80 microns. The nucleus was round, oval, indented or multiple. These cells were markedly phagocytic with vacuoles containing engulfed cells, possibly bacteria, and unidentified material in all stages of disintegration. With Giemsa stain marked fine azurophilic granulation of the cytoplasm was observed. By supravital staining from six to seventy or more granules were noted in the segregation apparatus.

2. Intermediate forms varying from the cells just described to normal appearing transitional cells (monocytes) were observed.

3. Their fluctuations were rapid but without periodicity and varied from 0 to 48 per cent. They varied directly with the number of platelets (in the case of E. W. especially), inversely with the bleeding time and decreased at the time of death. There was an increase from three to fifteen hours after transfusion. The fluctuations were evidently not associated with changes of temperature, pulse, respiration, digestion or sudden changes of physical or mental status.

4. Certain deductions are made as to origin, cause of production and release, mode of removal and function of these cells through parallelisms of their behavior with similar cells produced experimentally.

5. It is hoped that certain criteria, such as segregation apparatus and azurophilic granulations, will be used on a large number of cases of mononucleatoses to aid in the recognition and classification of the group of cells herein discussed.

PRIMARY CARCINOMA OF THE THYMUS*

VICTOR C. JACOBSON, M.D.

ALBANY, N. Y.

Primary tumors of the thymus are uncommon. Primary carcinoma is an exceedingly rare variety of thymic new growths, hence any definitely established neoplasm of this type should be recorded. A few years ago I had the opportunity of studying a case of carcinoma of the thymus, arising from Hassall's corpuscles, with metastasis to many organs. It is from the clinic of Dr. Henry A. Christian, to whom I am indebted for his permission to use the clinical data.

REPORT OF CASE

History.—The patient, a salesman, aged 42 years, entered the hospital Sept. 21, 1920, complaining of pain and stiffness in the lower part of his back. He was well up to June 1, 1920, when his back low down felt stiff and sore on rising in the morning. After moving around an hour or two, this stiffness and soreness left, only to return in the evening. The diurnal remissions grew gradually shorter, and on June 10 he was so stiff and lame that he had to stop working. The right side of his chest and abdomen was tender on pressure and movement.

His condition was diagnosed muscular rheumatism by his local physician. His back was strapped and after seven days in bed he felt slightly improved. There was no fever, redness or swelling. Six treatments by an osteopath gave some relief and he went back to work August 1 and continued working until September 7.

Gradually increasing stiffness of the back and hips, and pain radiating from the back around the right side made work impossible. The pain was intense and continuous, keeping him awake nights. During the last four months he lost about 10 pounds in weight. In the last six days there has been marked hoarseness and for two days his hands have felt stiff.

Physical Examination.—The patient is well developed and nourished and mentally clear. The pupils are prominent and there is bilateral, slow, rotary nystagmus. The optic disks and sight are normal. There are no cervical enlargements. Chest expansion is normal. The blood pressure is: systolic, 110; diastolic, 70. Coarse piping râles are heard over the right side of the chest. The spine is very rigid, especially in the lower dorsal and lumbar regions. There is tenderness on attempt at movement but none under pressure. At the lower dorsal level there is a rather sharp kyphosis. Both legs are stiff at the hips and there is a bilateral Kernig sign. The knee jerks and Achilles reflexes are active and equal. The gait is very slow, the back being held rigid, and the hips move very little. Skin sensation is normal to rough tests.

Two weeks later the lungs were normal to percussion, respiratory sounds were exaggerated throughout. There was slight bronchial breathing at the right base behind. No signs of bone involvement, other than in the spine, were elicited. The patient's temperature was usually normal in the morning, rising to about 99.5 F. in the afternoon. The urine was repeatedly negative for Bence-Jones protein. A surgical consultant regarded the condition as one of metastatic cancer, primary focus unknown, but said that if pyelograms did not

* From the laboratory of pathology of the Peter Bent Brigham Hospital, Boston.

indicate a hypernephroma the patient should be treated for tuberculosis, the slight fever corresponding better with cancer than with tuberculosis. The pyelograms were negative.

Clinical Course.—The pain in the lower limbs became lancinating during the day and morphin was necessary. An orthopedic consultant made a diagnosis of Pott's disease of the tenth dorsal and third lumbar vertebrae. A plaster jacket was applied to the spine October 25, but the pain in the limbs became more severe. Temperature by mouth varied from 98 to 101 F. A bone graft operation was advised as being the most efficient and shortest means of producing immobilization of the diseased area.

November 8 the patient went home wearing his plaster jacket. He was to rest a week before returning for operation. He returned on the twenty-ninth with numerous bed sores and having lost much weight. December 9 an anterior shell was applied.

His temperature rose at times to 99.6 F., pulse, 130. The pain became gradually worse, requiring morphin two or three times in twenty-four hours. He soon became short of breath for the first time. His temperature fell to subnormal. Respirations were shallow and difficult. Death occurred Feb. 9, 1921.

Report of Roentgen-Ray Examinations (Dr. Lawrence Reynolds).—Sept. 24, 1920: Lumbar spine in an anteroposterior position shows a rotation of the fourth and fifth lumbar vertebrae. There is a slight scoliosis. The chest is slightly asymmetrical and the diaphragm is normal in contour, with the tracheal shadow a bit toward the right of the midline. Root shadows show considerable increase in their density. The type of increase is suggestive of glandular enlargement. There are some rather extensive areas of infiltration, far out in the lung fields on the left side, suggestive of possible metastasis.

September 30: Dorsal spine in anteroposterior and lateral positions shows definite destruction of the tenth dorsal vertebra with partial destruction of the third lumbar vertebra. The position suggests a metastatic rather than a tuberculous condition.

October 21: A reexamination of the spine over the region of the eleventh dorsal and the third lumbar vertebrae shows a small shadow of increased density about the eleventh dorsal which is possibly an abscess, but the third lumbar shows some increase in its destruction.

December 1: The spine still shows the destructive process in the tenth dorsal vertebra. The chest is slightly asymmetrical with definite rotation toward the right side. There is marked increase in the density of the root shadows over the previous examination, and the lung fields themselves are much more extensively involved. The type of involvement still suggests, from a roentgen-ray point of view, metastasis to the lungs with involvement of the mediastinal and hilic glands.

Dec. 31: The chest shows rather extensive mediastinal involvement which is more marked than at the last examination.

Jan. 7, 1921: Films of the dorsal spine in the anteroposterior and lateral positions show destruction of the tenth dorsal vertebra. The amount of destruction is about the same as at the last examination. The lung fields show no change since the last examination.

Pathologic Report (Necropsy performed one hour postmortem).—Anatomic Diagnoses: Carcinoma of the thymus with widely disseminated metastases; kyphotic deformity of the spine due to destruction of the tenth thoracic and third lumbar vertebrae by tumor; nephrolithiasis, left; acute appendicitis; hemorrhoids. There was metastasis to the lungs, liver, spine, suprarenals, chest and retroperitoneal lymph nodes.

Mediastinum: The organs in the anterior mediastinum are closely apposed to the sternum. There is general infiltration of the areolar and fatty tissues by a fibroid growth. Lying in the position normally occupied by the thymus is a mass extending from the level of the aortic ring to 1 cm. above the sternoclavicular joints. Its inferior two-thirds appears to consist of cysts,

being fluctuant and of a dark color, which is transmitted through the thin capsule, suggesting, at first, markedly dilated veins. Incision permits the escape of a thin, brownish turbid fluid, under some pressure, disclosing a multilocular cystic growth, forming a chain of about four cysts which vary in size from 1 to 2 cm. They are lined with a white, glistening membrane. Bordering these cysts is grayish-white tissue, very firm, and divided into fairly well defined lobules much in the manner of a thymus. This whole mass

Fig. 1.—Drawing of the condition found in the anterior mediastinum. The thymus contains many cysts which increase in a moderate degree its antero-posterior dimensions. The mediastinal fat has been dissected away.

strips away from the underlying structure much as the thymus does normally. It continues 1 cm. above the level of the clavicle but is not adherent to the thyroid, which is quite normal. There are discrete, enlarged lymph nodes in the mediastinum lying posteriorly and beneath the medial ends of the

clavicles. Some of these are 2 by 1 by 1 cm. They are pale white, very firm, and consist almost entirely of tumor.

The pericardial cavity and heart are not remarkable. The great vessels are not involved in the tumor growth.

Lungs: Together the lungs weigh 1,675 gm. They are voluminous, with a moderate degree of emphysema of the anterior portions of the right and left upper lobes. The pleural surfaces are studded with grayish-white nodules averaging 6 mm. in width, which project slightly above the surface. Many of these lie in dilated lymph channels and are covered with a thin layer of fibrin. In freeing the right lung some parenchyma infiltrated with tumor is torn away and left attached to the parietal pleura. On section both lungs show extensive involvement. About the right hilum firm white tumor tissue is concentrated in mass and spreads out into the more peripheral portions in a more or less fanlike manner. Peribronchial infiltration by tumor is conspicuous throughout both lungs. The lymph nodes at the hilum are markedly enlarged because of tumor.

Spine: The tenth thoracic vertebra is about 1 cm. in thickness, having been practically replaced by a tumor growth which extends outward on both sides

Fig. 2.—Photograph of a section of the right lung showing the massive tumor infiltration proceeding outward from the hilum; also the perivascular and peribronchial metastases.

covering about one half of the anterior and lateral surfaces of the adjoining vertebrae, much in the manner of a mushroom. The body of the third lumbar vertebra is 2 cm. in thickness and is also surrounded by a dense tumor growth extending to the right about 3 cm. and practically covering the lateral surfaces of the second and fourth lumbar vertebrae. It does not appear to invade the intervertebral disks. The growth, both in the thoracic and lumbar levels, extends posterior to the bodies as well and there is considerable softening of the posterior lamellae of these vertebrae, but nothing of the nature of an abscess can be found. The tumor involving these vertebrae is pale white, very gritty and definite spicules of bone are deeply embedded in it, even in the growth farthest away from the body of the vertebra itself.

Microscopic Examination.—Thymus: The outlines of the organ can be made out in the sections, there being a distinct thin connective tissue envelop. Lobular divisions are fairly well defined in some sections, wide septums of connective tissue separating it into these units which are composed in great part of fat. In some of the lobules are foci of thymic lymphocytes, mononuclear

phagocytes (hemosiderin) and numerous eosinophils, surrounding one or two normal appearing Hassall's corpuscles. Other similar foci show a proliferation of the cells of Hassall's corpuscles with the formation of bodies three or four times the size of the normal. Degeneration of the cells in these bodies follows the normal picture, there being loss of nuclei, granulation and a sort of keratinization of the central cells. This is of progressively less prominence in the larger groups and assumes an entirely different aspect in the ones to be described. The proliferation of the epithelial cells forms bodies as much as ten times the size of the smallest groups, and in these a central lumen appears and papillary ingrowths occur.

The cysts seen in the gross are lined by more or less flattened epithelial cells in layers of from two to four. No intercellular bridges are seen. Slight

Fig. 3.—A longitudinal section through the spine showing the replacement of the tenth dorsal vertebra by a tumor which spreads out laterally in a mushroom-like manner. The vertebra has collapsed to about one-third its normal height.

recent hemorrhage has occurred in the walls, and hemosiderin is present between the cells in some places. A thin layer of rather compact fibrous tissue surrounds the epithelial lining, except where the cells have invaded it. Invasion of the surrounding areolar and fatty tissue from the concentric groups of epithelial cells and from the epithelium of the cysts is very striking in all the sections. The cells proceed in thick cords and often have a narrow lumen.

Accompanying these outgrowths are many cells resembling small lymphocytes, numerous eosinophils and phagocytes filled with hemosiderin. These cells surround small Hassall's bodies which have begun to proliferate and

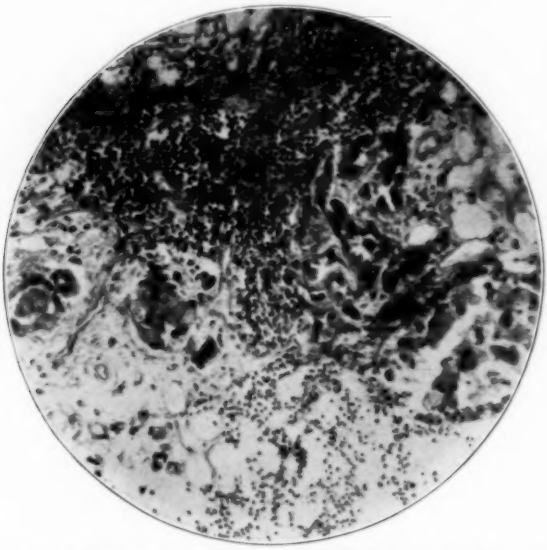

Fig. 4.—Photomicrograph of the thymus showing the malignant change in the epithelial bodies which in places tend to form cysts.

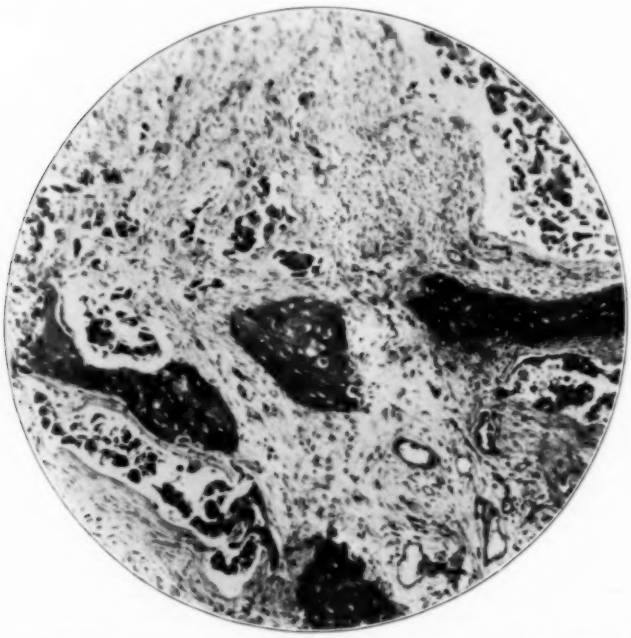

Fig. 5.—Photomicrograph of a section from the mushroom-like growth about the tenth dorsal vertebra.

among them are slightly larger polyhedral cells with pale ovoid nuclei, probably the reticulum cells. These are comparatively few and show no transitions which might indicate that they are part of the neoplastic growth. The stroma of the tumor is composed of numerous blood vessels and connective tissue in small amount, partly derived from the adventitia of the blood vessels. Invasion of both blood and lymph capillaries has occurred. Mitotic figures are numerous. As the tumor forms large conglomerate masses the cells assume the form of a syncytium with six to eight round nuclei, irregularly placed, the cytoplasm frequently appearing splashed with brilliant red, blue or both, with eosin-methylene blue staining. The architecture of the thymus is still unmistakable. The lobules while containing much fat have small Hassall's corpuscles surrounded by thymic lymphocytes. The various stages from the primary proliferation of the cells of the concentric bodies to the large epithelial tumor masses and epithelial lined cysts can easily be traced in the sections.

In the lung, of chief interest are the peculiar degeneration changes in the tumor cells and a frequent interfolding of tumor cells in such a way as to suggest very strongly a Hassall's corpuscle. The nucleus is round or ovoid and large, being one third to one half the size of the cell and with one to three deeply eosin-staining nucleoli. The cytoplasm presents a bizzare coloring, either deep blue or red or purple, and in it are frequently present round, deeply colored bodies about the size of the nucleus, usually with a halo or clear space about them. The nucleus is usually much shrunken or absent in the cells in which these bodies are found.

Spine: The mushroom-like growth on the side of the tenth dorsal vertebra consists of tumor in which are numerous trabeculae of new bone which undoubtedly arose from proliferation of the periosteum associated with extension of the tumor through it into the surrounding tissues. The tumor cells in these sections show the same peculiar staining properties and arrangement seen in the other metastases.

DISCUSSION

To better understand the development of tumors in the thymus gland a knowledge of its embryology is helpful. The thymus in man arises from the entoderm entirely, but in other animals it is from other sources, according to Zotterman.[1] In the mole it is purely ectodermic. In the pig it is of mixed origin. In the fowl isolated portions of striated muscle can be found, also cysts lined by ciliated epithelium. In man the thymus develops from two tubular outgrowths from the third pharyngeal pouches, although it is possible, according to Schäfer,[2] that a part may be derived from the fourth pouch. The reticulum differs from that of a lymph gland in being essentially formed of a syncytium of branched cells which are not mesodermic but entodermic, being formed from the cells of the original epithelial tube and thus have a common origin with Hassall's corpuscles. Some writers have asserted that the thymic lymphocytes are also of entodermic origin (Stöhr,[3] Bell[4]), but Hammar[5] and Maximow[6] found that the

1. Zotterman: Anat. Anz. **38**: 1911.
2. Schäfer: Quain's Anatomy; Textbook of Microscopic Anatomy **2**:676, 1912.
3. Stöhr: Anat. Heffte **31**: 1906.
4. Bell: Am. J. Anat. **5**: 1916.
5. Hammar: Anat. Anz. **26**: 1905.
6. Maximow: Arch. f. mikr. Anat. **74**: 1909.

lymphocytes are brought to the developing gland and are not formed there primarily.

Proliferation of the cells of Hassall's corpuscles is practically never seen in the normal thymus but it has been observed in a case of exophthalmic goiter reported by Soupault,[7] and in one of hemophilia by Acland.[8] Cysts of the thymus may arise in several ways. Persistence of the epithelial canals of the embryonal thymus is said to be a frequent cause of cysts in syphilitic infants (Ewing;[9] Pollossin and Piery,[10] and Chiari[11]). In Soupault's case there were also found multiple cysts lined by columnar epithelium. Dermoid cysts are reported by Hare, and a case of mixed tumor is recorded by Rolleston.[12] Hassall's corpuscles may be found in otherwise normal glands to have degenerated so as to form cysts barely visible to the naked eye, the "abscesses of Dubois." These cysts are probably comparable in many ways with epithelial cysts seen elsewhere, in the urinary tract for instance (Jacobson[13]).

Primary tumors of the thymus offer some difficulties in classification. Lymphosarcoma and malignant thymoma are terms commonly used to designate a tumor composed chiefly of cells resembling reticulum cells, although the small lymphocyte also is present in great numbers. This tumor usually penetrates the capsule and invades contiguous organs. These neoplasms of "lymphoid" type form the largest tumors taking origin in the thymus but they remain local or tend to keep within the bounds of the mediastinum. As a rule, this has been true also of the carcinomas, as most cases have shown no metastases, and no symptoms developed until the tumor had assumed considerable size.

To be correct, from the standpoint of embryology, the tumors definitely proved to arise from the cells of Hassall's corpuscles or the reticulum cells should be called carcinomas. The epithelium may be definitely pavement, cubical or cylindrical in type. The histologic picture of many thymus tumors is confused by the presence of many types of cells, lymphocytes, giant cells, eosinophils and plasma cells, in addition to cells of epithelial origin. Consequently, a diagnosis of carcinoma of the thymus is less frequently made than possibly it should be. Only two cases have appeared in the American literature, thirteen in the French and the rest have been described by the English and Germans, twenty-one, all told.

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7. Soupault: Bull. Soc. Anat. **592**: 1897.
8. Acland: Proc. Path. Soc., London **36**:491.
9. Ewing: Neoplastic Diseases, Philadelphia, W. B. Saunders Co., 1921, p. 891.
10. Pollossin and Piery: Prov. méd., 1901, p. 151.
11. Chiari: Ztschr. f. Heilk. **15**:403, 1894.
12. Rolleston: J. Path. & Bacteriol. **4**:228, 1896.
13. Jacobson: Bull. Johns Hopkins Hosp. **31**:122, 1920.

According to Rubaschow,[14] who himself reported a mixed epithelial and lymphoid tumor in 1911, the first diagnosis of carcinoma of the thymus was made by Bristowe in 1854. The next cases appeared in 1867, and between 1890 and 1908 all the French cases were observed. The age incidence differs from that for epithelial neoplasms of other organs. Fifteen patients were of "cancer age," but the six others were persons from 18 to 22 years of age. Fourteen cases were in males, three in females; in four cases the datum as to sex is not available. The early involution of the thymus, as compared with other organs, and its peculiar interrelationships with the thyroid, and possibly other glands, place it in a somewhat different category and probably explain the relatively high percentage of tumors of the thymus in younger persons.

In three of the earliest observations no metastases are mentioned. Lung metastases were present in the cases of Cayley,[15] Le Tulle[16] (Case 1), Ambrosini[17] (Case 2), and Symmers and Vance.[18] Direct extension into overlying lung tissue was noted by Paviot and Gerest,[19] and by Bruch[20] who also found invasion of the mediastinal lymph nodes. In the second case of Le Tulle's there was growth into the superior vena cava, and into the pericardium in those of Cayley and Ambrosini (Case 1). In only two instances was tumor found elsewhere than in the chest, and this was in the second case of Ambrosini's, in which nodules were present in the liver, and in the case of Symmers and Vance. The case reported here is the second showing metastasis to the spine, Symmers and Vance having the first, and the invasion of other organs was more widespread than any case hitherto described.

The outstanding clinical features were the lack of local signs of thymus tumor and the predominance of symptoms referable to the destruction of several vertebrae. Roentgen-ray studies played an important part in the diagnosis and prognosis of the case. Despite the great bulk of lung tissue replaced by tumor, the patient had little respiratory distress until shortly before death. While he had also acute appendicitis, any pain or tenderness he might have had in the region of the appendix was probably masked by the constant severe pain caused by the tumor in and about the vertebral column. The ocular

14. Rubaschow: Virchows Arch. f. path. Anat. **106**:141, 1911 (quoting cases of Bristowe, Ericksen and Derselbe).
15. Cayley: Proc. Path. Soc. Lond. **19**:53, 1867.
16. Le Tulle: Arch. gén. de méd. **2**:641, 1890.
17. Ambrosini: Thésè de Paris, 1894.
18. Symmers, Douglas, and Vance, B. M.; Epitheliomata of Thymic Origin, Arch. Int. Med. **28**:239 (Sept.) 1921.
19. Paviot and Gerest: Arch. méd. Exper. **8**:699, 1896.
20. Bruch: Prov. méd. **1**:267, 1904.

symptoms may have been due to cerebral metastases, but as the brain was not examined, this point could not be determined.

The thymus tumor itself was comparatively small, especially in its anteroposterior dimensions and could not reasonably be expected to cause much mechanical inconvenience. However, invasion of the lymph and blood streams occurred early, the tumor being brought to the lungs by the pulmonary artery. The distribution of the tumor in the lungs is quite typical of this route of entry, i. e., massive growth about the hila, smaller nodules in the more peripheral zones, and further dissemination through the perivascular and peribronchial lymphatics to the pleura. In the lungs, tumor cells gained entrance to the pulmonary veins, thus reaching the systemic circulation, thence to the spine, liver and suprarenals.

This tumor was derived from the concentric epithelial groups of the thymus—the so-called Hassall's corpuscles. The reticulum cells played no recognizable part in making up the growth. Very little lymphoid tissue was present in the thymus; the lobules were still largely made up of fat which had replaced thymus tissue in the usual manner and probably at a normal time.

The degeneration phenomena in the cells of the tumor in the thymus and most of the metastases were very bizarre and might be said to be an exaggeration of the peculiar changes seen in the epithelium of normal thymus glands. There was also a tendency for the metastases to form structures resembling Hassall's corpuscles.

SUMMARY

1. The commonest tumors of the thymus gland are those of the so-called lymphoid type. Tumors derived from epithelial tissue are rare, although probably not so rare as the literature indicates. Such tumors can arise from (*a*) Hassall's corpuscles, or (*b*) the reticulum cells. This concept has a sound embryologic basis.

2. A study of a case of carcinoma of the thymus in a man, aged 42, with clinical, roentgenologic and pathologic findings in detail, is presented. Emphasis is laid on the difficulty of an antemortem diagnosis because of the manner of metastasis to lungs and spine, which simulated tuberculosis in several of its aspects.

3. From a pathologic point of view, of greatest interest are the peculiar degeneration changes in the nucleus and cytoplasm of the tumor cells in the thymus and in the secondary growths, changes which might be construed as an exaggeration of what occurs in normal Hassall's corpuscles. Also in the metastases the tumor cells sometimes tended to arrange themselves in groups suggesting Hassall's corpuscles.

STOKES-ADAMS' DISEASE DUE TO GUMMA OF THE HEART*

RALPH H. MAJOR, M.D.

KANSAS CITY, KAN.

Although heart block is no longer regarded as a rare disease, its association with a gumma of the heart is still of such infrequent occurrence as to merit the report of every case observed. In 1905 only three titles appeared in the Index Medicus on the subject of Stokes-Adams disease. In 1906 there are forty-six references to this disease, the result of interest excited by the work of Kent, His, Tawara and Erlanger. During the succeeding years a large number of articles on heart block appear. A total of 499 papers have been published from 1903 to 1922.

The number of such cases proved to be due to a gumma of the heart is quite small. Keith,[1] in 1909, collected seven cases, and Hirschfelder,[2] in 1913, also collected seven cases. I have been able to find only eleven cases in the literature up to 1922, those of Rendu,[3] Handford,[4] Keith and Miller,[5] Grünbaum,[6] Ashton, Norris and Lavenson,[7] Fahr[8] (also reported by Luce[8]), Vaquez and Esmein,[9] Heineke, Müller and Hösslin,[10] Robinson,[11] Bridgman and Schmeisser[12] and Girdwood.[13]

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*From the Department of Internal Medicine, University of Kansas School of Medicine.

1. Keith, A.: Albutt's System of Medicine **6**:133, 1909.
2. Hirschfelder, A.: Disease of the Heart and Aorta, 1913, p. 566.
3. Rendu, M.: Note sur un cas de syphilis du coeur accompagnée de pouls lent permanent, Bull. et mém. soc. méd. d. höp. de Par. **12**:381, 1895.
4. Handford, Henry: Remarks on a Case of Gummata of the Heart, Brit. M. J. **2**:1745, 1904.
5. Keith, A., and Miller, C.: Description of a Heart Showing Gummatous Infiltration of the Auricular Ventricular Bundle, Lancet **2**:1429, 1906.
6. Grünbaum: Quoted by Hirschfelder, Footnote 2.
7. Ashton, T. G.; Norris, G. W., and Lavenson, R. S.: Adams-Stokes Disease (Heart Block) Due to a Gumma in the Interventricular Septum, Am. J. M. Sc. **152**:1745, 1907.
8. Fahr: Ueber die muskuläre Verbindung zwischen Vorhof und Ventrikel (das Hissche Bundel in Normalen Herzen und beim Adams-Stokesschen Symptomkomplex), Virchows Arch. f. path. Anat. **188**:562, 1907.
9. Vaquez and Esmein: Maladie de Stokes-Adams par lesion sclerogommeuse du faisceau de His (Herzblock), Presse méd. **15**:57, 1907.
10. Heineke, A.; Müller, A., and Hösslin, H.: Zur Kasuistik des Adams-Stokesschen Symptomkomplex und der Ueberleitungstörungen, Deutsch. Arch. f. klin. Med. **93**:459, 1908.
11. Robinson, G. Canby: Gumma of the Heart from a Case Presenting the Symptoms of Adams-Stokes Disease, Bull. Ayer Clin. Lab., No. 4, 1, 1907.
12. Bridgman, E. W., and Schmeisser, H. C.: Heart Block Caused by Gumma of Septum, Johns Hopkins Hosp. Rep. **18**:90, 1919.
13. Girdwood, R. L.: Case of Heart Block Due to Gumma, M. J. South Africa **16**:183, 1921.

The presence of a gumma in the heart associated with symptoms of Stokes-Adams disease is referred to by some earlier writers who failed through imperfect knowledge of the pathology of heart block to realize the significance of such association. Rendu's patient, who had a "permanent slow pulse," showed at necropsy a gumma the size of a pigeon's

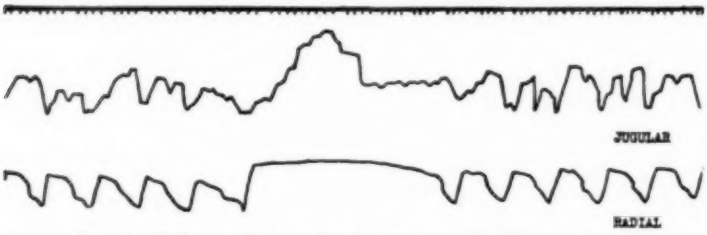

Fig. 1.—Pulse tracing made during an epileptiform attack.

Fig. 2.—Photograph of heart with incision through the right ventricle. The gumma can be seen on the interventricular septum.

egg in the wall of the left ventricle. However, small granular kidneys were also found, and Rendu attributed the bradycardia to "uremic intoxication" of renal origin. Phillips,[14] in 1897, collected twenty-five

14. Phillips, S.: Syphilitc Disease of the Heart Wall, Lancet **1**:223, 1897.

cases of gumma of the heart, and he mentions syncope and epileptiform attacks as being frequent symptoms of the disease. Some of these cases were probably examples of Stokes-Adams' disease.

The case of heart block due to a gumma of the heart here reported is apparently the twelfth on record.

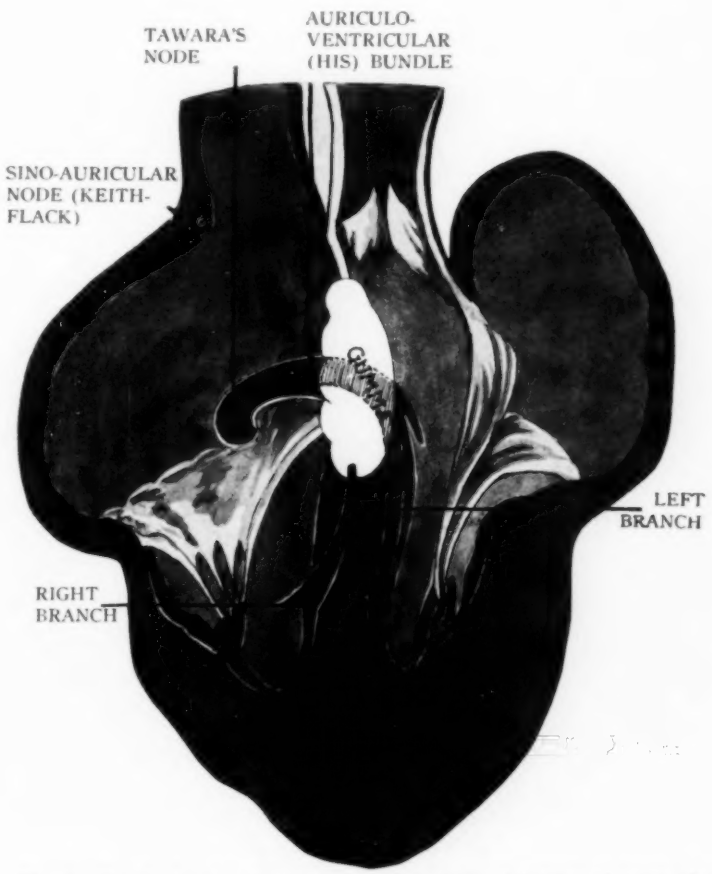

Fig. 3.—Sketch showing the position of the gumma (diagram of heart after Hirschfelder).

REPORT OF CASE

The patient was a man, aged 34, a farmer, who was admitted to the medical service of the Bell Memorial Hospital complaining of shortness of breath and weakness.

Family History.—His father died of "heart trouble," the exact nature of which was unknown.

Personal History.—This was negative. There was no history of rheumatic infection or of syphilis.

Present Illness.—Two months before admission, the patient, while working in the field, suddenly became unconscious. This attack lasted about ten minutes. A few minutes following the attack he felt perfectly well and was able to continue his work. The next day he had a similar attack, and for six weeks he

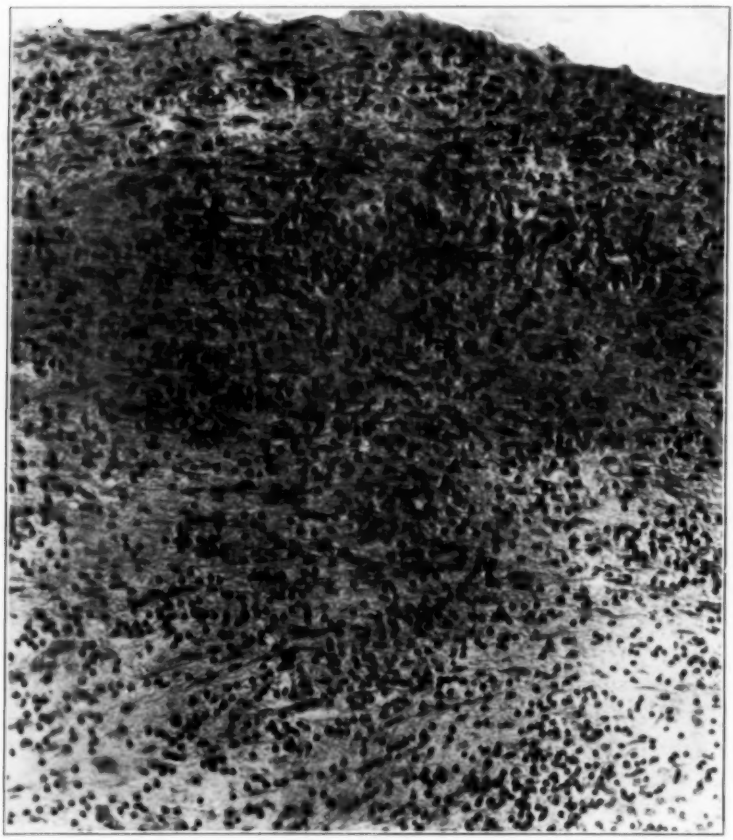

Fig. 4.—Microscopic section through gumma (Bausch and Lomb obj. 4 oc., × 10.

had one or two such attacks a week. The past two weeks before admission the attacks became much more frequent, until at the time of admission he had several attacks a day.

Physical Examination.—The heart was found to be enlarged, extending 14 cm. to the left in the fifth interspace and 5 cm. to the right in the fourth interspace. On auscultation, there was a blowing systolic murmur at the apex, and at the base there was a loud blowing systolic murmur and a somewhat softer blowing

diastolic murmur. These murmurs were equally well heard at the aortic and pulmonary areas and almost completely replaced the heart sounds. The pulse was of good volume, not collapsing and the rate varied from 42 to 60 per minute. The radials were not thickened, and the blood pressure was 125 systolic and 80 diastolic. The lungs were clear; there was no ascites or edema of the extremities. The reflexes were normal.

Clinical Course.—While in the ward the patient had many epileptiform seizures, varying in number from eight to ten per day. These attacks lasted from five to ten seconds. The patient was unconscious; his face twitched; his eyes rolled up and were staring, and his arms and legs were stiffly extended. During these attacks the pulse could not be felt at the wrist, although the jugular pulse in the neck continued to beat.

A tracing (Fig. 1) taken during one of these attacks shows a complete absence of the radial waves while the jugular pulse records several *a* waves. Both before and after this attack the tracing shows no evidence of any block, and the pulse rate was 60 per minute. One tracing showed a two to one rhythm but all the other tracings taken showed a normal rhythm with periods of complete block corresponding to the patient's epileptiform attacks. All tracings showed a prolongation of the *a-c* interval, the time usually being two-fifths of a second.

Laboratory Examination.—The blood cell count was: red cells, 5,000,000; white cells, 10,000; hemoglobin, 90 per cent. The urine was normal. The Wassermann reaction was positive.

Treatment.—The patient was given hypodermics of atropin and strychnin but was not observed long enough to permit of drawing any conclusion in regard to the value of these drugs. The patient died seven days after admission, during an epileptiform attack, and the necropsy was performed the following day by Dr. Wahl.

REPORT OF NECROPSY (BY DR. WAHL)

The heart was enlarged and weighed 670 gm. The coronary arteries showed no sclerosis. On palpation of the heart indurated masses were felt at the bases of the aortic and pulmonary valves. When the heart was opened, a yellowish mass measuring 5.5 by 2 by 2 cm. was seen in the interventricular septum (Fig. 2) extending up to the base of pulmonary valves. It also extended into the base of the aortic valve and involved two of the aortic leaflets. This mass bulged out into the cavity of the right ventricle and protruded also into the left ventricle. It completely obliterated the triangular space, went directly across the right branch of the bundle of His, pressed on the left branch and extended nearly up to the auricular ventricular node (Fig. 3). On cut section this mass was yellowish in color, somewhat granular and resembled a gumma.

The anatomic diagnosis was: gumma of the heart; aortic stenosis; aortic insufficiency; pulmonary stenosis; pulmonary insufficiency; hypertrophy and dilation of the heart, syphilitic aortitis.

Microscopic sections taken from the mass (Fig. 4) showed a typical gumma.

This specimen resembles very much that described by Ashton, Norris and Lavenson, Robinson, Bridgman and Schmeisser and by Girdwood. The large size of the gumma is noteworthy as are the combined aortic and pulmonary lesions produced by it. The mitral systolic murmur described by Goodall as an almost invariable accompaniment of heart block was present here, but was not so marked as the systolic and diastolic murmurs originating at the base of the heart.

HYDROGEN-ION STUDIES. VII. EXPERIMENTAL NEPHRITIS IN RABBITS WITH MONOBASIC SODIUM PHOSPHATE *

EDWIN F. HIRSCH, M.D.

CHICAGO

Many studies of experimental nephritis are reported in the literature, notably those which concern the injection of the salts of the heavy metals, uranium and tartrates, into rabbits and dogs. There seems to be no mention of nephritis caused by the injection into rabbits of relatively large amounts of monobasic sodium phosphate. In the course of certain experiments with rabbits, injections of solutions of this salt were made and in the examination of the kidney tissue, necrosis of the cells lining the convoluted tubules and the loops of Henle was observed. Other experiments were made to confirm this observation, and in each instance depending in severity largely on the length of time that the rabbit was poisoned by the injections, there are necrotic changes in the cells of the renal tubules mentioned. Blood to be used for determining the hydrogen ion concentration and the carbon dioxid combining power was drawn from the heart through a sterile needle into a 10 c.c. defibrinating tube, all of the air being displaced. After defibrination by shaking, the hydrogen ion concentration of the blood was determined in a McClendon electrode vessel by the gas chain method. The carbon dioxid combining power of the whole blood was determined according to Van Slyke and Cullen.[1]

PROTOCOLS OF EXPERIMENTS

The protocols for two typical experiments are given.

EXPERIMENT 1.—A rabbit weighing 2,470 gm. was used. The urine was normal.

June 14, 1922: 9 a. m., bled; p_H, 7.57; carbon dioxid, 51.18 per cent. by volume.

2 p. m.: injected subcutaneously 10 c.c. 20 per cent. solution of monobasic sodium phosphate.

June 15: 9:30 a. m., bled; p_H, 7.41; carbon dioxid, 48.29 per cent. by volume.

11 a. m.: 6 c.c. injected subcutaneously.

12:30 p. m.: 8 c.c. injected subcutaneously.

2:30 p. m.: Death; bled; p_H, 7.04; carbon dioxid, 27.10 per cent. by volume. Urine contains a large amount of albumin, hyaline and granular casts, leukocytes, and a few red blood cells.

EXPERIMENT 2.—A rabbit weighing 1,310 gm. was used. The urine was normal.

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* From the Pathological Laboratory of St. Luke's Hospital. Aided by the Winfield Peck Memorial Fund.

1. Van Slyke, D. D., and Cullen, G. C.: Studies of Acidosis, I, J. Biol. Chem. **30**:289-346, 1917.

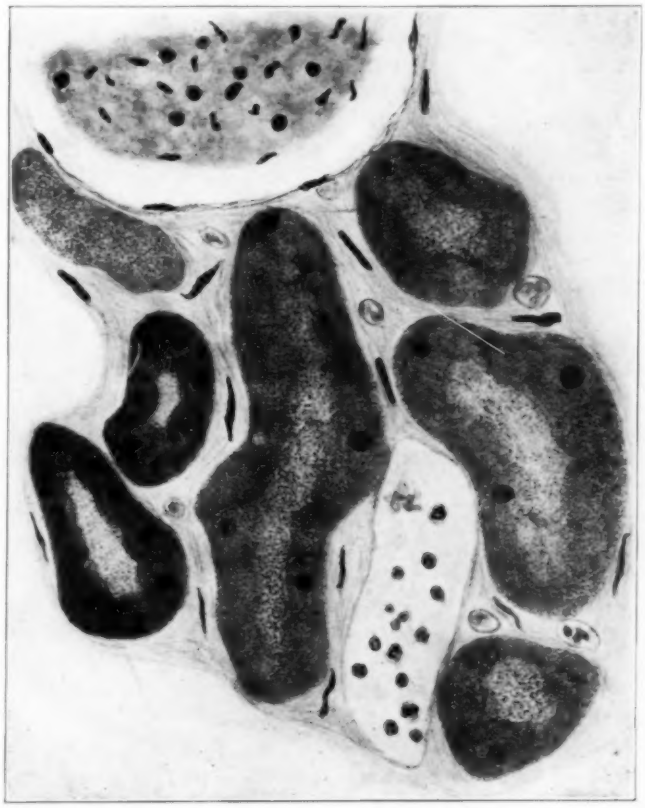
June 26, 1922: 9 a. m., bled; p_H, 7.40; carbon dioxid, 53.93 per cent. by volume.

3:30 p. m.: Injected subcutaneously 5 c.c. 20 per cent. solution of monobasic sodium phosphate.

June 27: 9 a. m.: 4.5 c.c. was injected subcutaneously. The urine contains albumin, hyaline casts, and a few leukocytes.

4 p. m.: 4.5 c.c. injected subcutaneously.

June 28: 9 a. m.: 5 c.c. was injected subcutaneously. Urine contains albumin, many granular casts and cylindroids.



Sketch illustrating necrosis of the convoluted tubules of the rabbit kidney following the injection of monobasic sodium phosphate solutions.

June 29: 10 a. m., 7.5 c.c. injected subcutaneously.

June 30: 11:30 a. m., 9.5 c.c. injected subcutaneously.

July 2, 9 a. m.: Urine contains a trace of albumin, a few granular casts and cylindroids.

July 3: 10 a. m., 10 c.c. was injected subcutaneously.

3 p. m., 4 c.c. was injected intravenously. Rabbit dead. Blood carbon dioxid 12.14 per cent. by volume.

The changes in the kidney tissues, are most marked in the cells of the convoluted tubules, but are present also to a lesser degree in those of the loops of Henle. These changes are chiefly a necrosis of the epithelium, the cytoplasm of the cells becoming at first swollen and granular, then, with prolonged poisoning they become necrotic, so that only fragments of the basal portions and pyknotic nuclei of the cells remain. Within the lumen of the tubules there is a granular amorphous substance (precipitated albumin) in which there are occasional renal cells and polymorphonuclear leukocytes. The cells of Henle's loops and of the convoluted tubules contain fine dustlike droplets which stain with sudan III. These degenerative changes are like those observed by Wells [2] in rabbits the victims of tartrate poisoning.

DISCUSSION

Injury of the renal epithelium by the administration of the monobasic sodium phosphate probably is associated with the excretion of this salt by the kidneys. McNider,[3] Karsner [4] and others have observed an acidosis occurring with nephritis experimentally produced by salts of uranium. According to Fischer [5] acid bodies are important in a variety of pathological changes, particularly in nephritis. Karsner, however, regards the acidosis accompanying uranium poisoning not the direct cause of the renal irritation. Theoretically, an acidosis may be expected to follow the injection of an acid salt, and the results of such experiments may be considered the effect of the acidosis. However, the blood of a rabbit injected with 10 c.c. of a 20 per cent. dibasic sodium phosphate solution changed in reaction from p_H 7.40 to p_H 6.80; the carbon dioxid combining power changed from 41.32 per cent. by volume to 25.27 per cent.; the urine contained albumin, casts and a large amount of sugar, and death ensued rapidly. The cell changes in the kidney sections of this rabbit also resemble those produced by the injection of the monobasic phosphate solutions. This suggests a much more profound disturbance in the general metabolism than merely the absorption and elimination by the kidneys of a salt injected subcutaneously.

The phosphate salts of sodium and potassium have a wide clinical use, and that large amounts may be injurious to kidney tissue is suggested by the experiments reported here. It is known that with certain

2. Underhill, F. P.; Wells, H. G., and Goldschmidt, S.: Tartrate Nephritis, J. Exper. Med. **18**:322-346, 1913.

3. McNider, Wm. deB.: The Inhibition of Toxicity of Uranium Nitrate by Sodium Carbonate, etc., J. Exper. Med. **23**:171-186, 1916.

4. Karsner, H. J., etc.: Studies of Uranium Poisoning. IV. The Relation of Acid Intoxication to Nephritis, J. M. Research **39**:177-187, 1918.

5. Fischer, M. H.: Edema; a Study of the Physiology of Water Absorption by the Living Organism, New York, 1910.

patients the use of large amounts of phosphates is accompanied by the sudden appearance of albumin, casts and red blood cells in the urine. These manifestations of kidney injury may be regarded as the result of the use of the phosphate salts mentioned.

SUMMARY

The subcutaneous injection of monobasic sodium phosphate solutions causes in rabbits a necrosis of the cells lining the convoluted tubules and the loops of Henle.

An acidosis accompanies the injection of solutions of this salt.

Symptoms of an acute nephritis in patients receiving large amounts of phosphates may be due to changes in kidney tissue similar to those observed in rabbits.

THE DILATATION OF THE PULMONIC AREA OF THE HEART AND ITS SIGNIFICANCE

JAMES A. HONEIJ, M.D.

BOSTON

If the diagram representing the frontal view of the heart outlines, as shown on the fluoroscopic screen or by roentgenograms, is studied, several curves and depressions are noticed. The right side of the heart presents a single convex curve caused almost wholly by the auricle; the left side presents usually two curves, the superior curve caused by the aorta and the greater and inferior curve caused by the left ventricle. Between these two curves, situated usually between the second and third ribs, is a depressed line or concavity.

In this area, in abnormal conditions of the heart, the pulmonic artery and a portion of the auricle below it can sometimes cause two smaller curves instead of the normal depression. Or, frequently, a single marked curve is noticeable, so that the left side of the heart may show three noticeable curves instead of two. This third curve, if it covers the whole area, is caused by the dilatation of the pulmonic artery and auricle or to the pulmonary artery alone. This area is, then, commonly spoken of as the pulmonic area. On the right side there is never seen but one curve unless there is dilatation or an aneurysm of the ascending portion of the aorta.

In studying the changes in the heart three groups of cases must be kept in mind. The diagnosis of these cases may directly concern the heart or indirectly the lungs. By saying indirectly the lungs, I mean that the heart changes very frequently assist one in diagnosing the acuteness of the pulmonary lesion and sometimes assist in the prognosis of the lesion.

For some years I have been interested in the cardiac outlines in pulmonary conditions but not until the influenza epidemic of 1918, when I had the privilege of studying the cases at U. S. Army General Hospital No. 16, did I realize the importance of the changes of the heart outlines in acute pulmonary conditions.

It is well known that dilatation of the right auricle occurs in pulmonary congestion and in children it is an important concomitant sign, but very little attention has been paid to the dilatation of the pulmonic area in pulmonary affections.

The dilatation of this area in cardiac diseases is well known. In mitral insufficiency and stenosis this area is markedly dilated.[1] In pulmonary insufficiency complicating mitral disease, the pulmonic raea forms a beautiful curve, distinct in most cases from the auricle curve

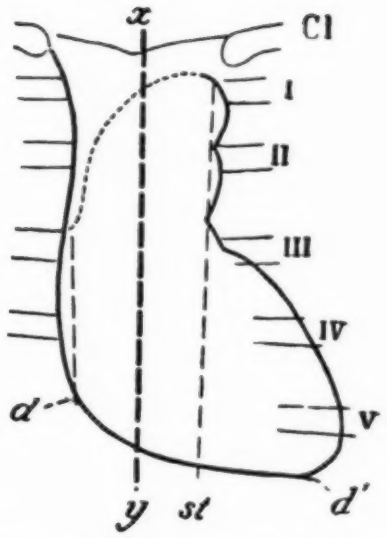


Fig. 1.—The normal cardiac outlines, with slight accentuation of the pulmonic curve, showing between the second and third ribs. The aortic curve between the first and second ribs and the curve of the ventricle between the third and fifth ribs.

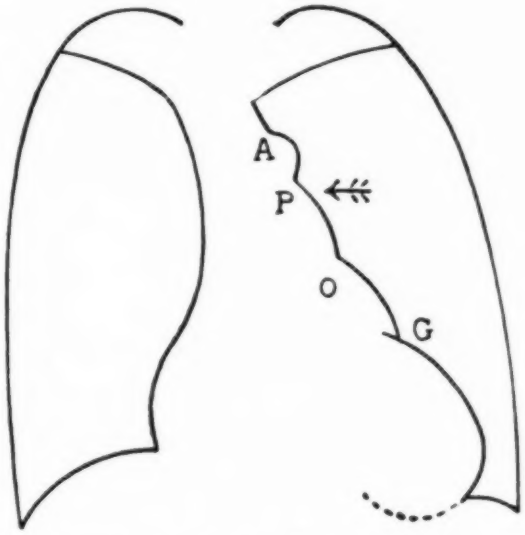


Fig. 2.—The abnormal cardiac outlines. *A*. Aortic curve. *P*. Pulmonic curve. *O*. Auricle curve. *G*. Ventricle curve. The case represents a pulmonary insufficiency complicating mitral disease.

which is also pronounced. Stell, as quoted by Vaquez and Bordet, called attention to this and associated changes and states that mitral lesions, especially stenosis, could provoke, following increase of pressure in the smaller vessels, an insufficiency of the pulmonary orifice of functional nature. So also in congenital pulmonary stenosis and in conditions of interventricular perforation and in other cardiac conditions. Such conditions, however, have no relation to any extent to pulmonary conditions, with the exception of cardiac pulmonary insufficiency and myocarditis.

In pulmonary conditions this pulmonic curve very early becomes pronounced. Some time ago I [1] pointed out that in influenza "the heart shows a slight dilatation of the right auricle and, to a less extent, a

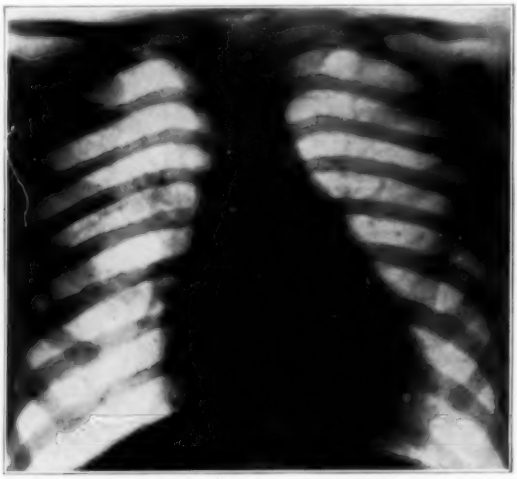


Fig. 3.—Dilatation of the pulmonic area in a child without discernible cause.

slight dilatation of the pulmonic area," and in pneumonia "'two associated changes occur very early which are of great interest and importance. Invariably, as early as the changes occur in the hilus, there is seen in the heart a marked and acute dilatation of the pulmonic area." During the epidemic, necropsy findings constantly included the observation of the noticeable dilatation of the right auricle, but, no notice, or little, was apparently taken of the pulmonic area.

It can be accepted, therefore, that dilatation of the right auricle and to a less extent the pulmonic area, is known to be associated with acute pulmonary conditions.

1. Honeij, J. A.: Influenza and Bronchopneumonia. Am. J. Roentgenol. **6**: 266 (May) 1919.

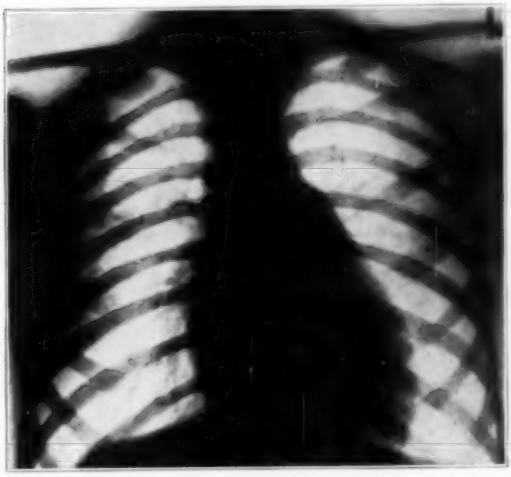


Fig. 4.—Dilatation of the pulmonic area of a child without discernible cause.

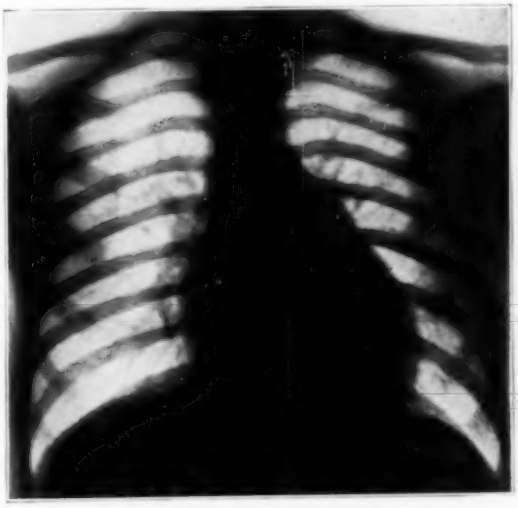


Fig. 5.—Dilatation of the pulmonic area in a child without discernible cause.

The third general class of cases of dilatation of the right auricle is associated with pulmonary tuberculosis. In many of these cases I have seen some dilatation of the pulmonic area, especially in children. In a series of twenty-five cases, in children under 16 years of age, which were being studied for tracheobronchial gland changes, and in which only two cases of cardiac disease occurred, I have noticed dilatation of the pulmonic area in thirteen. The cause of this cannot at the present time be considered to be pulmonary congestion, as in most cases there was no apparent congestion. It might be assumed at this time that gland pressure and congestion may probably be an associated cause.

It is well known that some dilatation of the heart and of the pulmonic area can be produced physiologically by repeated coughing without inspiring, but why dilatation of the pulmonic area occurs when there is apparently no pulmonary stress is a question that needs studying. It is well worth while to consider this concomitant sign in interpreting roentgenograms of chests. It may be transitory and in many cases it is progressive.

Recently Bishop [2] published an article in which he quotes Vaquez and Bordet [3] as follows: "Vaquez and others have come to our rescue in their observations in this one particular, namely, that a very distinct dilatation in the region of the conus, meaning an enlargement of the pulmonary artery, showed no corresponding post-mortem condition by the methods employed in such work up to the present time. In fact, the examination of the right side of the heart and pulmonary circulation is, as a rule, carried out carelessly." Further on in this article, the author states, that "the fluoroscope usually shows besides a centrally located heart shadow, a fairly definite predominance in the region of the conus." It is evident that the author in making a diagnosis of "infantile heart" obtains part of his evidence from the roentgenogram showing a dilatation of the pulmonic area, for besides his statements he concludes his article thus, "the illustration is a typical example of an infantile heart in an adult."

I can only say that without precise cardiac measurements, or positive absence of pulmonary changes or absence of postmortem proof, the "infantile heart in adult life" cannot be considered seriously. This is purely from the roentgenographic point of view of the abnormal cardiac outlines.

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2. Bishop, L. F.: The Infantile Heart in Adult Life, Boston M. & S. J. **187**:23 (July 6) 1922.

3. Vaquez and Bordet: The Heart and the Aorta, translated by James A. Honeij and J. Macy.

OBSERVATIONS ON THE BLOOD GASES IN AURICULAR FIBRILLATION AND AFTER THE RESTORATION OF THE NORMAL MECHANISM *

HAROLD J. STEWART, M.D.

BALTIMORE

The object of this investigation was to determine what changes take place in the gases of the arterial and venous blood when the cardiac mechanism reverts from auricular fibrillation to the normal mechanism. There has been no report of similar studies in the literature, and, indeed, such studies were hardly possible, except in the uncommon condition of paroxysmal fibrillation, until quinidin sulphate was found to bring about the restoration of the normal mechanism in auricular fibrillation.

In the studies which Harrop [1] made of the blood gases there are reported two cases of auricular fibrillation with determinations of the gases of the arterial and venous blood during decompensation and after the patients became compensated. Peters and Barr [2] give the carbon dioxid absorption curves and blood gases in two cases of auricular fibrillation in their studies on cardiac dyspnea. Lundsgaard [3] has included several cases of auricular fibrillation in his report on the oxygen of the venous blood in patients with compensated and decompensated circulatory disturbances. Barach [4] has studied oxygen therapy in two cases of auricular fibrillation. In none of these cases, however, is there a return to the normal mechanism.

All the patients included in this study were put to bed on admission and, if there were any signs of cardiac failure, a standard tincture of digitalis [5] was administered up to the point of maximum benefit before the quinidin therapy was begun.

Control samples of arterial and venous blood were usually taken after digitalization. The patient was then given a preliminary dose of 0.2 gm. quinidin sulphate to determine any idiosyncrasy. If there was no untoward reaction to the preliminary dose, the patient was started on larger doses (0.4 gm.), given from three to five times a day. The

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* From the Physiological Division of the Medical Clinic of the Johns Hopkins University and Hospital.

* Working under the tenure of the William Bingham Fellowship in Medicine.

* Abstract read before the American Society for Clinical Investigation, Washington, May, 1922.

1. Harrop, G. A. J. Exper. Med. **30**:241, 1919.
2. Peters, J. P., and Barr, D. P.: J. Biol. Chem. **45**:559, 1921.
3. Lundsgaard, C.: J. Exper. Med. **27**:179, 199, 219, 1918.
4. Barach, A. L.: Arch. Int. Med. **28**:367 (Sept.) 1921.
5. One c.c. of the tincture is equivalent to 1 cat unit.

drug was continued until there was some indication for discontinuance. The arterial and venous samples of blood were obtained after the onset of the normal mechanism. Control galvanometric records were frequently taken.

METHODS

The arterial and venous samples were drawn without stasis under liquid petrolatum as described by Stadie [6] for arterial blood and by Lundsgaard [7] for venous blood. In a total of about one hundred arterial punctures there was no untoward effect; in most instances the patients said the arterial puncture did not cause any greater discomfort than the venipuncture. Procaine was used only in a few cases. Usually, the arterial blood was drawn before the venous blood, but in the case of persons in whom the most accessible vein and artery were in the same arm, the venipuncture was done first in order to avoid the stasis brought about by pressure applied after the arterial puncture. In some persons the radial artery was used, and in others the brachial artery. The patients in whom both the radial and the brachial artery were punctured preferred the brachial puncture. One of the veins at the bend of the elbow was used for the venous blood. The arterial and venous samples were drawn within from three to five minutes of each other. The venous blood was sometimes drawn in a syringe [6] and at other times in a pipet.[7] The analyses were done in duplicate immediately after the blood was drawn. The earlier analyses were done with the original type of Van Slyke apparatus, using the Van Slyke methods for determining the carbon dioxid [8] and oxygen [9] of the whole blood. Later the "giant" Van Slyke apparatus was used, the pipet of which is twice the length and approximately one half the bore of that of the original apparatus, and is calibrated to 0.01 c.c. instead of 0.02 c.c. The Van Slyke and Stadie [10] method for determining oxygen and carbon dioxid in the same sample was used. In all analyses the new corrections for the oxygen and nitrogen physically dissolved in the blood were used. When oxygen and carbon dioxid were done on separate specimens of blood, the order of analysis was as follows: venous carbon dioxid, arterial carbon dioxid, venous oxygen, arterial oxygen and oxygen capacity of the arterial blood. When the combined method was used, the venous blood was analyzed first, then the arterial blood and lastly the oxygen capacity was determined.

The samples of blood were drawn at least two hours after the previous meal, after the patient had been lying at absolute rest for half

6. Stadie, W. C.: J. Exper. Med. **30**:215, 1919.
7. Lundsgaard, C.: J. Biol. Chem. **33**:133, 1918.
8. Van Slyke, D. D.: J. Biol. Chem. **30**:347, 1917.
9. Van Slyke, D. D.: J. Biol. Chem. **33**:127, 1918.
10. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **49**:1, 1921.

an hour or longer. After the patients left the hospital they returned for frequent observations, the same precautions being taken in obtaining the samples. Pulse and respiration rates were recorded during both the arterial and venipunctures. The blood pressure, galvanometric record and vital capacity were taken either just before the rest period or immediately after the blood was drawn.

During fibrillation the average systolic blood pressure was determined after the method of James and Hart.[11] The normal vital capacity was calculated from West's formula [12] according to which the normal vital capacity is 2.5 litres per square meter of body surface area in men, and 2 litres per square meter of body surface in women. The body surface area was estimated from the height-weight chart of Du Bois and Du Bois.[13] The vital capacity is recorded as percentage of the normal.

GROUPING OF CASES

Fifteen cases of auricular fibrillation have been studied. Fourteen of these patients received quinidin sulphate; in twelve there was reversion to the normal mechanism. The cases have been divided into the following groups.

GROUP I.—Nine cases studied during fibrillation and after the restoration of normal mechanism.

GROUP II.—Two cases, which were studied after reversion to normal mechanism, but in which no analyses were made in the presence of fibrillation.

GROUP III.—Four cases studied during fibrillation but not during normal mechanism.

REPORT OF CASES

GROUP I

CASE 1 (2) (Tables 1 and 2).—Patient was a female, white, aged 63 years, who was admitted to the hospital, Nov. 2, 1921. She was discharged, improved, Dec. 7, 1921. Mechanism was normal.

History.—Three years ago patient had her first attack of cardiac failure. Three subsequent attacks of cardiac failure occurred.

Examination.—There was slight edema of the feet and ankles; no dyspnea; no cyanosis; a few râles at the bases posteriorly; the liver was enlarged. The heart was slightly enlarged; the rhythm was totally irregular; a systolic murmur heard at the apex was transmitted to the axilla. A systolic murmur was heard in the second right interspace, and faintly heard in the neck vessels. The Wassermann test was negative.

Diagnosis.—Arteriosclerosis; hypertension; myocardial insufficiency; auricular fibrillation.

Treatment.—Nov. 3 and Nov. 4, 1921, the patient received digitalis, bringing the heart rate down to 64, with a pulse deficit of 4. November 8, the patient reverted to a normal mechanism. November 11, she reverted to fibrillation, and

11. James, W. B., and Hart, T. S.: Am. J. M. Sc. **147**:63, 1914.
12. West, H. P.: Arch. Int. Med. **25**:306 (March) 1920.
13. Du Bois, D., and Du Bois, E. F.: Arch. Int. Med. **17**:863 (June) 1916.

November 13 the normal mechanism was again restored. The patient was discharged with a normal rhythm, which was still present when she was last seen in May, 1922.

This case shows an increase in the oxygen saturation [14] of arterial and venous blood and a diminution of the coefficient of utilization with the onset of the normal mechanism, which indicates an improvement in the blood flow. There was a persistent anoxic anoxemia,[15] except on one occasion. There was no apparent cause for this arterial anoxemia. Dec. 19, 1921, when the arterial blood was 100 per cent. saturated, the venous saturation was 94 per cent., and the venous blood was as bright red as the arterial. The oxygen consumption and the oxygen capacity were both decreased. A progressive improvement in the vital capacity was seen. The cause for the venous (stagnant) anoxemia December 5, in the presence of the normal mechanism, is not clear, but it was felt at the time that the patient probably had been going beyond her cardiac reserve and might be on the verge of cardiac failure, although she showed no clinical signs of failure. There was great subjective improvement in the patient with the normal mechanism and since leaving the hospital she has been doing her own work without the occurrence of dyspnea or edema.

Case 2 (9) (Tables 1 and 2).—Patient was a man, white, aged 29 years, whose first admission was Nov. 7, 1921. He was discharged, Dec. 3, 1921, with a normal mechanism. Second admission was Feb. 28, 1922. Patient was again discharged, March 11, 1922, with a normal mechanism.

History.—Patient complains of lack of vitality and endurance. He had influenza in 1918. Since then he has had his present symptoms. Oct. 15, 1921, an electrocardiogram showed auricular fibrillation.

Examination.—There were no signs of cardiac failure. The heart was not enlarged; the rhythm was totally irregular, with the apex rate 60, and a pulse deficit of a few beats. There were no murmurs. The Wassermann test was negative.

Diagnosis.—Chronic myocarditis; slight myocardial insufficiency; auricular fibrillation.

Treatment.—Digitalis was not necessary. November 10, administration of quinidin sulphate was begun and the patient reverted to normal mechanism the same day with no subjective improvement. November 18, the patient reverted to fibrillation and November 20 normal mechanism was again restored, and was present on his discharge. December 16, the patient had reverted to fibrillation. He was readmitted with an apex rate of 72 and a pulse deficit of 12. Quinidin sulphate administration was begun, and the patient reverted to normal mechanism, March 1. He was discharged with a normal mechanism, but returned again fibrillating and was given quinidin daily. March 24, fibrillation was still present and the dose of quinidin was increased. March 31, normal mechanism was found, which was still present April 10, when the patient asked to be allowed to discontinue the use of quinidin.

14. Arterial saturation and venous saturation in the text refer to the per cent. arterial oxygen saturation and per cent. venous oxygen saturation, respectively.

15. Barcroft, J.: Lancet **1**:487, 1920.

This is a case of probable rheumatic heart disease, with as yet very slight structural change, but functionally there is some impairment of cardiac reserve. This case shows an increase in the venous oxygen saturation and a decrease in the coefficient of utilization with each fluctuation from auricular fibrillation to the normal mechanism, indicating an improvement in the circulation. There is a decrease in the arterial oxygen saturation after the onset of the normal mechanism, with the first two reversions from fibrillation to normal mechanism, but in the third reversion the arterial saturation rose to 100 per cent. Nevertheless, the patient showed no subjective improvement with the normal mechanism, although the discomfort caused by the quinidin sulphate might have masked any such improvement. It is interesting to note the extremely high vital capacity of this patient, and its rise following the onset of normal mechanism. From Table 1 it is seen that the oxygen capacity diminishes with the onset of the normal mechanism, increases when fibrillation begins and decreases each time with the normal mechanism. The high hemoglobin content during fibrillation is noteworthy. The oxygen consumption diminished with the onset of the normal mechanism.

CASE 3 (Tables 1 and 2).—Patient, male, white, aged 77 years, was admitted, Nov. 30, 1921, and discharged, Dec. 14, 1921, improved and with a normal mechanism.

History.—Auricular fibrillation was discovered in a routine physical examination made July 8, 1919. He has had no acute cardiac failure. He had received a small amount of digitalis just before admission.

Examination.—There were no signs of cardiac failure, but signs of senile emphysema. The heart was not enlarged; the rhythm was totally irregular. At the apex, the first sound was accompanied by a soft systolic murmur. A presystolic gallop was present. The radials were tortuous and thickened.

Diagnosis.—Arteriosclerosis; emphysema; myocardial degeneration; auricular fibrillation.

Treatment.—Digitalis was not necessary. The patient reverted to normal mechanism, December 5. December 9, the electrocardiogram showed auricular flutter. December 11, normal mechanism was again present. The patient was discharged with a normal mechanism.

This patient was much improved subjectively by the reversion to the normal mechanism. With the change to the normal mechanism the venous saturation increased, and the coefficient of utilization diminished. There was a decrease in the arterial saturation immediately after reversion to the normal mechanism, which later returned to the normal level. The patient's emphysema did not prevent normal saturation of blood with oxygen in the lungs, except on two occasions when there was a slight anoxic anoxemia. The oxygen consumption was decreased; the oxygen capacity was first slightly increased then appreciably diminished and later, when iron was administered, it increased again. This

TABLE 1.—Changes in Blood Gases in Auricular Fibrillation and After Reversion to Normal Mechanism. Cases of Group I

Case No.	Diagnosis	Date	Mechanism	Vital Capacity, per Cent. Normal	Oxygen Content		Oxygen Saturation		Coefficient of Utilization, per Cent.	Oxygen Consumption, Volume per Cent.	Oxygen Capacity, Volume per Cent.	Hemoglobin, per Cent.	Carbon Dioxid		Blood Pressure
					Arterial Volume per Cent.	Venous Volume per Cent.	Arterial, per Cent.	Venous, per Cent.					Arterial, Volume per Cent.	Venous, Volume per Cent.	
1 (2)	Arteriosclerosis, hypertension, myocardial insufficiency, auricular fibrillation	11/ 7/21	Aur. Fib.	58	11.49	8.43	84.3	61.9	22.4	3.06	13.63	73.6	.....	.....	184 mm.
		11/ 8/21	Normal	58	10.75	8.66	91.8	74.0	17.8	2.09	11.71	63.5	42.64	47.49	220 90
		11/21/21	Normal	61	11.30	8.27	90.8	66.5	24.3	3.03	12.44	67.2	54.48	57.48	180/95
		12/ 5/21	Normal	71	10.24	4.00	81.7	31.9	49.8	6.24	12.54	67.8	47.15	52.96	
		12/19/21	Normal	71	11.54	9.88	100.0*	94.5	5.5	1.66	10.46	56.5	43.32	45.61	208/98
		2/ 7/22	Normal	82	10.51	9.03	87.7	75.3	12.4	1.48	11.99	64.8	60.09	61.76	180/90
2 (9)	Chronic myocarditis, slight myocardial insufficiency, auricular fibrillation	11/ 9/21	Aur. Fib.	110	19.94	16.10	96.8	78.2	18.6	3.84	20.59	111.3	31.37	37.69	93 mm.
		11/12/21	Normal	136	16.24	14.48	95.1	84.2	10.9	1.76	17.08	92.3	37.25	43.86	120/85
		12/16/21	Aur. Fib.	134	17.38	9.46	99.0	53.9	45.1	7.92	17.56	94.9	41.24	47.63	
		1/13/22	Aur. Fib.	125	21.01	10.81	92.7	47.7	45.0	10.20	22.67	122.5	50.50	59.20	
		2/ 3/22	Aur. Fib.	130	22.72	12.01	98.1	51.9	46.2	10.71	23.15	125.1	51.29	64.86	
	Second admission.....	2/28/22	Aur. Fib.	126	22.46	11.13	97.1	48.1	49.0	11.33	23.13	125.0	47.41	62.91	95 mm.
		3/ 1/22	Normal	128	19.60	14.86	92.5	70.1	22.4	4.74	21.19	114.5	52.23	60.80	125/90
		3/ 4/22	Normal	...	.....	13.62	.....	65.1	....	.....	20.91	113.0			
		3/24/22	Aur. Fib.	122	21.13	13.05	96.0	59.4	36.6	8.08	22.01	119.0	58.18		
		3/31/22	Normal	127	21.23	12.18	100.0†	57.9‡	42.1	9.05	21.03	113.7	51.43	66.70	135/85
		4/ 6/22	Normal	130	.....	16.02	.....	68.4	....	.....	23.42	126.6	.....	62.50	110/70
3 (3)	Arteriosclerosis, emphysema, myocardial degeneration, auricular fibrillation	12/ 1/21	Aur. Fib.	52	16.08	12.32	98.4	75.4	23.0	3.76	16.35	89.5	50.65	56.44	118 mm.
		12/ 6/21	Normal	61	16.80	16.48	94.4	92.6	1.8	0.32	17.79	96.2	39.56	42.22	130/80
		12/ 8/21	Normal	63	15.74	13.65	100.0*	91.9	8.1	2.09	14.85	80.3	41.88	42.33	135/70
		12/14/21	Normal	64	15.00	14.45	100.0*	96.2	3.8	1.14	14.91	80.6	37.70	38.85	130/80
		12/21/21	Normal	58	13.60	13.28	95.9	93.6	2.3	0.32	14.18	76.7	42.99	43.34	140/80
		1/ 6/22	Normal	63	12.89	12.73	93.4	92.3	1.1	0.16	13.80	74.9	39.94	41.19	
		1/20/22	Normal	68	15.58	14.09	100.0†	91.3	8.7	1.34	15.43	83.4	52.12	53.08	140/80
		2/14/22	Normal	61	17.65	16.14	95.8	85.9	7.9	1.51	18.81	101.7	52.48	53.14	160/90
		3/ 2/22	Normal	56	16.84	13.63	92.1	74.6	17.5	2.21	18.28	98.8	54.37	56.34	140/85
		3/30/22	Normal	63	16.27	.....	97.7	....	....	.....	16.65	90.0	54.49	.....	150/85
		3/31/22	Normal	...	.....	15.82	.....	87.8	....	.....	18.02	97.4	.....	59.02	

4 (5)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, auricular fibrillation	12/20/21	Aur. Fib.	50	9.05	3.90	100.0*	46.0	54.0	5.15	8.47	45.7	43.11	49.08	92 mm.
		1/ 4/22	Normal	87	8.19	3.78	92.8	42.8	50.0	4.41	8.83	47.7	43.90	46.35	120/70
		2/ 1/22	Normal	87	10.62	4.71	98.1	43.5	54.6	5.91	10.83	58.5	55.20	58.62	140/80
		2/18/22	Normal	82	10.96	7.22	94.5	68.2	32.3	3 74	11.60	62.7	49.89	52.83	130/75
		3/25/22	Normal	89	12.18	7.78	96.9	61.9	35.0	4.40	12.57	67.9	54.36	59.84	130/70
5 (10)	Arteriosclerosis, emphysema, myocardial insufficiency, auricular fibrillation	1/13/21	Aur. Fib.	...	15.64	4.88	94.6	29.5	65.1	10.76	16.54	89.4	53.67	62.34	182 mm.
		1/31/22	Normal	...	15.50	15.15	90.4	88.4	2.0	0.35	17.14	92.7	56.25	57.26	130/86
		2/ 6/22	Normal	...	15.91	14.72	90.1	83.5	6.7	1.19	17.65	95.4	55.71	59.83	
		2/ 9/22	Normal	...	14.32	12.93	88.3	79.8	8.5	1.39	16.21	87.6	54.32	57.14	
6 (7)	Exophthalmic goiter, cardiac hypertrophy and dilatation, myocardial insufficiency, auricular fibrillation	2/ 3/22	Aur. Fib.	38	17.85	9.38	93.6	49.2	44.4	8.47	19.07	103.1	51.49	60.75	88 mm.
		2/11/22	Normal	44	17.46	11.60	91.7	60.9	30.8	5.86	19.04	102.9	60.37	61.91	144/92
		2/21/22	Normal	60	18.52	7.38	100.0†	39.4‡	60.6	11.24	18.43	99.6	59.32	68.55	130/60
		2/24/22	Normal	...	.....	15.46	.....	85.8	....	.....	18.02	97.4	.....	58.78	
		3/ 8/22	Normal	...	.....	9.57	.....	65.1	....	....	14.70	79.5	.....	58.85	
		3/27/22	Normal	64	14.68	10.18	97.1	67.1	30.0	4.58	15.02	81.1	55.25	61.68	135/60
7 (8)	Arteriosclerosis, chronic pulmonary emphysema, cardiac hypertrophy, myocardial insufficiency, auricular fibrillation	4/13/22	Aur. Fib.	48	19.66	14.94	91.5	69.6	22.0	4.72	21.48	116.1	62.26	66.10	160 mm.
		4/18/22	Normal	63	17.22	16.34	89.9	85.3	4.6	0.88	19.16	103.6	62.85	66.43	110/55
		4/23/22	Normal	67	17.67	.....	91.7	....	....	.....	19.27	104.2	63.06		
8 (4)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, auricular fibrillation	12/15/21	Aur. Fib.	36	17.81	15.13	94.3	80.1	14.2	2.68	18.89	102.1	38.36	38.82	80 mm.
		1/16/22	Normal	46	17.70	14.52	89.5	73.4	16.1	3.18	19.78	106.9	47.75	49.07	135/85
		3/ 1/22	Normal	42	.....	14.02	.....	69.1	....	....	20.30	109.7	.....	55.40	150/70
		3/22/22	Normal	47	19.72	15.10	96.8	74.1	22.7	5.62	20.38	110.2	55.44	61.14	130/78
9 (12)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, slight emphysema, auricular fibrillation	1/ 6/22	Aur. Fib.	40	14.04	8.65	93.7	57.8	35.9	5.34	14.98	81.0	39.92	45.92	102 mm.
		1/16/22	Normal	33	15.80	9.13	92.4	53.4	39.0	3.18	17.10	92.4	54.15	59.27	145/75
		1/30/22	Aur. Fib.	49	20.32	10.30	100.0*	52.7	47.3	10.02	19.55	105.4	56.52	68.08	92 mm.
		2/10/22	Aur. Fib.	68	18.88	10.37	95.1	52.2	42.9	8.51	19.86	107.4	53.75	63.74	

* Difference between arterial oxygen content and oxygen capacity is probably due to excess oxygen in physical solution. Oxygen capacities checked by saturating a second sample of blood.

† Difference between arterial oxygen content and oxygen capacity is within experimental error.

‡ Patient held arm stiff and made a fist, causing venous stasis.

§ Patient near an open window; cold and cyanotic.

TABLE 2.—CASES IN GROUP I

Case No.	Date	Pulse		Respiration		Artery Used	Digitalis	Quinidin Sulphate	Remarks
		Arterial Puncture	Venous Puncture	Arterial Puncture	Venous Puncture				
1 (2)	11/ 7/21	70	70	28	28	Left radial	6 c.c. tincture	.....	A few râles at bases, no edema
	11/ 8/21	60	60	22	22	Right radial	.....	.....	Marked subjective improvement
	11/21/21	66	58	24	24	Right radial	.....	10.5 gm.	
	12/ 5/21	58	60	22	24	Right radial			
	12/19/21	52	50	18	20	Right radial	.....	.....	Increasing cardiac reserve
	2/ 7/21	60	60	14	14	Right brachial	.....	.....	Continued improvement
2 (9)	11/ 9/21	64	58	16	16	Right brachial	0	.....	Lassitude. No signs cardiac failure
	11/12/21	78	76	14	14	Right brachial	.....	9.7 gm.	No subjective improvement
	12/16/21	60	70	20	16	Right brachial			
	1/13/22	58	64	18	20	Right brachial			
	2/ 3/22	56	68	14	16	Right brachial	.....	.....	Dyspnea after walking
2d Admission	2/28/22	64	60	12	14	Right brachial	0	Started again	Weakness. No signs cardiac failure
	3/ 1/22	72	76	14	12	Left brachial	.....	.....	No subjective improvement
	3/ 4/22	..	72	..	20				
	3/24/22	64	66	16	16	Left brachial	.....	15.6 gm.	
	3/31/22	64	72	16	14	Left brachial	.....	0.4 gm. Q. D.	Feels very tired and nervous
	4/ 6/22	..	54	..	14	.....	.....	.....	Asked to discontinue quinidin
3 (3)	12/ 1/21	60	66	24	26	Right radial	0	.....	No signs cardiac failure
	12/ 6/21	104	110	18	20	Right radial	.....	.....	Marked subjective improvement
	12/ 8/21	66	58	20	22	Right radial			
	12/14/21	76	80	22	24	Right radial			
	12/21/21	66	64	20	22	Right radial	.....	11.0 gm.	
	1/ 6/22	62	66	18	20	Right radial	.....	.....	Feels stronger. Cardiac reserve increased
	1/20/22	62	58	16	20	Right radial			
	2/14/22	60	56	16	16	Brachial			
	3/ 2/22	60	60	24	16	Right radial			
	3/30/22	60	..	16	..	Right radial			
	3/31/22	..	60	..	16				
4 (5)	12/20/21	72	66	20	16	Left brachial	0		
	1/ 4/22	76	70	20	14	Left brachial	.....	13.0 gm.	Marked subjective improvement
	2/ 1/22	80	72	22	22	Left radial	.....	.....	Some dyspnea and precordial pain
	2/18/22	90	72	24	32	Left brachial	.....	.....	Greatly increased cardiac reserve
	3/25/22	60	60	20	22	Left radial			
5 (10)	1/13/22	52	64	24	20	Right brachial	0	.....	Cyanosis. No edema, no râles
	1/31/22	100	100	..	..	Left brachial	.....	.....	Great subjective improvement. No cyanosis
	2/ 6/22	72	85	22	22	Left brachial			
	2/ 9/22	100	100	28	30	Left brachial	.....	10.8 gm.	Increased cardiac reserve
6 (7)	2/ 3/22	100	74	24	22	Left brachial	2.7 gm. leaves	.....	Râles at bases, cyanosis, dyspnea and edema
	2/11/22	80	80	26	26	Left brachial	.....	.....	Subjective improvement. Few râles. No dyspnea
	2/21/22	76	72	28	21	Left brachial	.....	.....	Patient near open window. Chilly and cyanotic
	2/24/22	..	72	..	20	.....	.....		
	3/ 8/22	..	76	..	21	.....	.....	23.4 gm.	
	3/27/22	78	80	22	20	Right radial	.....	.....	No signs cardiac failure. Increased cardiac reserve
7 (8)	4/13/22	56	48	18	16	Right radial	28 c.c. tincture	.....	Peculiar dusky cyanosis. No other signs cardiac failure
	4/18/22	48	46	18	20	Right radial	.....	.....	Only a slight tinge of cyanosis
	4/23/22	..	..	..	..	Right radial	.....	11.7 gm.	Increased cardiac reserve
8 (4)	12/15/21	120	110	..	..	Brachial	0	.....	No signs cardiac failure. Low cardiac reserve
	1/16/22	108	120	24	20	Brachial	.....	16.0 gm.	Marked subjective improvement
	3/ 1/22	...	104	..	24				
	3/22/22	90	86	26	24	Right brachial	.....	.....	Cardiac reserve increasing
9 (12)	1/ 6/22	88	72	28	28	Brachial	48 c.c. tincture	.....	Râles at bases, cyanosis, liver enlarged
	1/16/22	60	60	18	20	Brachial	.....	17.4 gm.	Slight cyanosis, few râles, no subjective improvement. Liver smaller
	1/30/22	64	60	20	21	Brachial	22 c.c. tincture	.....	No cyanosis, no râles
	2/10/22	80	70	18	18	Brachial	.....	2.0 gm. more	

increase may have been either a physiologic response to a demand for more hemoglobin or the result of iron therapy. The patient's vital capacity improved.

CASE 4 (5) (Tables 1 and 2).—Patient, a female, white, aged 38 years, was admitted, Dec. 19, 1921, and discharged, Dec. 31, 1921, improved and with normal mechanism.

History.—She had had rheumatism at 8 years. Her present illness began in May, 1920, with dyspnea on slight exertion. She was a dispensary patient from June to September, 1920. There were only occasional symptoms of cardiac failure during the period from September, 1920, to November, 1921, when there was a rather rapid decrease in cardiac reserve as shown by marked dyspnea, edema of the ankles and palpitation. The patient received digitalis in the dispensary.

Examination.—There were no signs of congestive heart failure. The heart was slightly enlarged to the left. A systolic thrill was noted at the apex. The rhythm was totally irregular. At the apex there was a short, high pitched, systolic murmur, and a low pitched rumbling murmur in middiastole. The liver was not felt.

Diagnosis.—Chronic rheumatic endocarditis; mitral stenosis and insufficiency; myocardial insufficiency; auricular fibrillation.

Treatment.—Digitalis was not necessary. December 22, the use of quinidin was begun, and on December 26 the patient reverted to normal mechanism, which was present on discharge and was still present when the patient was seen in April, 1922.

This patient showed evidence of marked structural cardiac change with rapidly diminishing cardiac reserve. With return to the normal mechanism, there was a great improvement subjectively and the cardiac reserve improved tremendously, so that the patient is now able to do all her own housework, without dyspnea, edema or palpitation. With the onset of the normal rhythm the arterial saturation was decreased, but the following analysis showed that it had returned to normal. There was an actual decrease in the venous oxygen saturation with the onset of the normal mechanism; but since the arterial saturation was decreased to a greater extent, the coefficient of utilization was diminished, showing an improvement in the circulation. The gaseous exchange of the blood thus took place on a lower level during the normal mechanism than during fibrillation. The cause for the venous anoxemia during the normal mechanism may have been the rather severe anemia which the patient had, for with the improvement of the anemia the venous saturation improved almost to the normal figure. The oxygen consumption was decreased. The vital capacity showed marked improvement.

CASE 5 (10) (Tables 1 and 2).—Patient, female, white, aged 73 years, was admitted, Jan. 11, 1922, and discharged, Feb. 13, 1922, improved and with normal mechanism.

History.—Symptoms began one year ago with dyspnea on exertion. Slight cough has been present since this time with occasionally some edema of the

ankles. She came to the dispensary in June, 1921, and was kept on digitalis from that time. September 10, an electrocardiogram showed auricular fibrillation. In the last month the dyspnea became worse.

Examination.—Patient was senile; she had slight dyspnea, but no cyanosis. There were signs of fairly marked emphysema, with congestion of the bases of the lungs. The heart was enlarged. The rhythm was totally irregular. Loud systolic murmur was heard over the base, and was well transmitted to the neck. The pulse was slow with a small deficit. The peripheral arteries were not thickened. There was no edema.

Diagnosis.—Arteriosclerosis; emphysema; myocardial insufficiency; auricular fibrillation.

Treatment.—Digitalis was not necessary. January 28, quinidin sulphate was begun, and January 30 the normal mechanism was restored. Late on January 31 fibrillation was present, reverting to the normal mechanism again February 3. Late on February 6 fibrillation began again, and February 8 normal mechanism was again restored. Normal rhythm was present on discharge.

This was a senile patient who had probably been fibrillating for one year, during which time her cardiac reserve gradually declined. She was improved clinically by the reversion to the normal mechanism. It is interesting to note the presence of an unusually high average systolic blood pressure (182 mm. mercury) during fibrillation. During the normal mechanism the blood pressure fell to 130 systolic and 86 diastolic. There was a decrease in the arterial saturation with the normal rhythm, which did not return to normal later, probably because of the high grade of emphysema. During fibrillation the blood flow may have been so slow that the blood remained in the lung capillaries long enough to become fully oxygenated in spite of the emphysema, but with the normal mechanism and the improved circulation rate this was not possible. The circulation was improved by the normal mechanism, as is shown by the greatly improved venous saturation and the diminished coefficient of utilization. The oxygen consumption was decreased and the oxygen capacity slightly increased.

The patient was again admitted to the hospital early in March, 1922, and was found to be fibrillating. No attempt was made to give quinidin on this admission, and the patient died of a cerebral accident a few days later.

Case 6 (7) (Tables 1 and 2).—Patient, a male, white, aged 58 years, was admitted Feb. 3, 1922, and discharged March 11, 1922, improved and with normal mechanism.

History.—Nervousness began in October, 1914. March 6, 1915, ligation of the right inferior thyroid artery was done. March 25, 1915, ligation of both superior thyroid arteries was done. May 5, 1915, an injection of boiling water was made into both lobes of the thyroid. June 1, 1915, a left lobectomy was made. The patient improved after operation. Jan. 24, 1916, a right lobectomy with partial excision of isthmus of the thyroid was made. The patient improved. Eighteen months after the last operation, the patient noticed a lump on the right side of his neck. He later became dyspneic and had palpitation. Three weeks ago he began to sleep propped up in bed and his eyes became prominent.

Examination.—He was a small, undernourished man, very nervous, with moist skin, cyanosis of lips, fingers and ear lobes. Exophthalmos was present, and a small lump on the right side of the neck. Râles were heard at the lung bases posteriorly. The heart was slightly enlarged. The rhythm was totally irregular. A soft blowing systolic murmur was transmitted feebly to the axilla. The apex beat rate was 140—deficit 18. The liver was 11 cm. below the costal margin. There was no edema.

Diagnosis.—Exophthalmic goiter, cardiac hypertrophy and dilatation, myocardial insufficiency, auricular fibrillation.

Treatment.—The patient was thoroughly digitalized, pulse rate continuing in the neighborhood of 120, with a pulse deficit of 18. February 8 the use of quinidin sulphate was begun and February 11 the patient reverted to normal mechanism. February 21 the basal metabolism was 49 per cent. above normal. February 28 radium treatment was given to the thyroid. March 5 the patient reverted to fibrillation. March 7 the normal mechanism again restored. The patient was discharged with a normal rhythm. The normal mechanism was still present when the patient was seen April 29, 1922.

This was a case of marked cardiac failure and auricular fibrillation secondary to toxic goiter. There was a most striking improvement clinically with reversion to the normal mechanism. His palpitation, dyspnea, edema and râles, which did not clear up under digitalis, disappeared under the normal mechanism. There was marked distress when he reverted to fibrillation for two days. He is now able to work again. The arterial saturation decreased with the onset of the normal mechanism and later returned to normal. The increase in the venous saturation and lowered coefficient of utilization show an improved circulation. There was a gradual decrease in the oxygen capacity. The oxygen consumption was diminished. There was a steady rise in the vital capacity.

Case 7 (8) (Tables 1 and 2).—Patient, a male, white, aged 57 years, was admitted April 5, 1922, and discharged April 23, 1922, improved and with normal mechanism.

History.—Two years ago, dyspnea on exertion was first manifested. About eight months ago, he stopped work because of increasing dyspnea and edema.

Examination.—He had a moderate cyanosis of his lips and finger tips, but no dyspnea. The jugulars were prominent and distended. Signs of a rather marked emphysema, and moist râles at lung bases posteriorly were noted. The heart was enlarged. A totally irregular rhythm and faint systolic murmur at the apex, not transmitted, were noted. The pulse was 64, with a deficit of a few beats. The vessels were thickened and tortuous. There was a fluid wave in the abdomen. The liver was 6 cm. below the costal margin. He had edema of the feet, ankles and legs up to the groin. The Wassermann test was negative.

Diagnosis.—Arteriosclerosis; emphysema; cardiac hypertrophy; myocardial insufficiency; auricular fibrillation.

Treatment.—From April 5 to April 13 digitalis was given, with disappearance of most of the edema. April 13 the use of quinidin sulphate was begun and April 16 the patient reverted to normal mechanism which was present on discharge.

This patient, with a "large lung" emphysema with auricular fibrillation, came into the hospital with a marked degree of heart failure, and under digitalis most of the edema disappeared. He showed marked improvement clinically with the onset of the normal rhythm and his cardiac reserve increased. There was a decrease in the arterial saturation which later increased again, although the normal limit was not reached, probably because of the marked emphysema. The venous saturation increased; the coefficient of utilization, the oxygen consumption and the oxygen capacity decreased. There was no change in the carbon dioxid content of the arterial or venous blood. It is interesting to note the high carbon dioxid content and capacity (78.21 volumes per cent.) of the venous plasma. Scott [16] has called attention to the high carbon dioxid capacity of the plasma in chronic pulmonary emphysema but has shown that there was no appreciable change in the p_H of the blood. Respiratory experiments carried out on this patient showed a high aveolar carbon dioxid and there was an improvement in the respiratory minute volume with the normal mechanism.

CASE 8 (4) (Tables 1 and 2).—Patient, female, white, aged 48 years, was admitted Dec. 12, 1921, and discharged Dec. 31, 1921, improved and with normal mechanism.

History.—Patient had an acute attack of rheumatic fever fourteen years ago; four years later she had a second attack with cardiac involvement. There was dyspnea on exertion, but she lived quietly and within her cardiac reserve, until January, 1921, when she overworked. In March, 1921, her heart began to beat rapidly and there was marked orthopnea. She was in bed for one month and took digitalis. Since then she has been in bed at intervals.

Examination.—There was slight cyanosis of lips, but no dyspnea. The heart was not enlarged. No thrill was present. Rhythm was totally irregular. A short systolic murmur and a short early diastolic murmur were heard at the apex. A few râles were heard at the bases of the lungs. Edema was absent. The Wassermann test was negative.

Diagnosis.—Chronic rheumatic endocarditis; mitral stenosis and insufficiency; myocardial insufficiency; auricular fibrillation.

Treatment.—Digitalis was not necessary. December 16 the use of quinidin sulphate was begun. It was discontinued December 19 because of nausea and abdominal pain. December 24 quinidin sulphate was used again and the patient reverted to normal mechanism. The patient was discharged with normal rhythm and it was still present in April, 1922.

This case showed an advanced structural cardiac change with almost no cardiac reserve at the time of admission. After reversion to the normal mechanism she was tremendously improved subjectively and the rhythm was still regular when she was seen in April, 1922. She was doing her own housework. After the onset of the normal mechanism, the arterial saturation decreased and later returned to normal. There was a decrease in the venous saturation and an increase in the coefficient of utilization under the normal rhythm. There was an increase in

16. Scott, R. W.: Arch. Int. Med. **26**:544 (Oct.) 1921.

oxygen consumption and in oxygen capacity and an improvement in the vital capacity.

CASE 9 (12) (Tables 1 and 2).—Patient, a male, white, aged 60 years, was admitted Jan. 5, 1922, and discharged Feb. 10, 1922, improved, but with auricular fibrillation.

History.—Dyspnea and palpitation began fifteen years ago, when digitalis was given. Dyspnea has gradually increased in severity with occasional orthopnea. Edema of ankles was present for three months. A cerebral accident two and one-half years ago resulted in an aphasia of a few weeks duration. A similar cerebral accident occurred in October, 1921, which left a permanent aphasia.

Examination.—Patient had a marked arteriosclerosis, dyspnea, marked cyanosis, chronic passive congestion of the lungs and some emphysema. The heart was enlarged, and the rhythm was totally irregular. A systolic apical murmur was transmitted to the axilla. Localized presystolic murmur was heard at the apex. The liver edge was palpable to the level of the umbilicus. There was no edema. The Wassermann test was negative.

Diagnosis.—Chronic rheumatic endocarditis; mitral stenosis and insufficiency; myocardial insufficiency; slight emphysema; auricular fibrillation.

Treatment.—From January 6 to 11 digitalis was given, bringing the cardiac rate to 65, with a pulse deficit of from 6 to 10 beats. January 12 the use of quinidin sulphate was begun, and on January 14 normal mechanism was restored. January 21 there was reversion to fibrillation and January 23 quinidin sulphate was discontinued because of rise in temperature and the presence of râles in the chest. Digitalis was then given. January 31 the use of quinidin was begun again but the patient had a chill with a rise in temperature and quinidin was discontinued. February 5 digitalis was started again. The patient was discharged with fibrillation still present.

This case of auricular fibrillation with cardiac failure was digitalized before quinidin sulphate was begun. Subjectively the patient was not improved by the normal mechanism, and later when he reverted to fibrillation he could not take quinidin without an unfavorable reaction. The slight anoxic anoxemia present during the fibrillation is accounted for by the pulmonary congestion. There was a further increase in the anoxic anoxemia with the onset of the normal mechanism, but February 10, after reversion to fibrillation, when there were no signs of pulmonary congestion, the arterial saturation was 100 per cent. The venous anoxemia and the coefficient of utilization increased, indicating that there was no improvement of the blood flow with the normal mechanism. There was a progressive rise in oxygen capacity which was probably a compensatory mechanism. The oxygen consumption increased. The vital capacity decreased but later improved on reversion to fibrillation.

GROUP II

CASE 10 (6) (Tables 3 and 4).—Patient, a male, white, aged 58 years, was admitted Jan. 3, 1922, and discharged Jan. 10, 1922, improved, and with normal mechanism.

History.—Dec. 7, 1920, the patient was awakened by a "pounding of his heart" lasting two hours, followed by dyspnea, weakness and edema of ankles.

TABLE 3.—Blood Gases in Cases of Groups II and III

Case No.	Diagnosis	Date	Mechanism	Vital Capacity, per Cent. Normal	Oxygen Content		Oxygen Saturation		Coefficient of Utilization, per Cent.	Oxygen Consumption, Volume per Cent.	Oxygen Capacity, Volume per Cent.	Hemoglobin, per Cent.	Carbon Dioxid		Blood Pressure
					Arterial Volume per Cent.	Venous Volume per Cent.	Arterial, per Cent.	Venous, per Cent.					Arterial, Volume per Cent.	Venous, Volume per Cent.	
10 (6)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, cardiac hypertrophy and dilatation, slight myocardial insufficiency, auricular fibrillation	1/ 5/22 1/10/22 1/17/22 2/ 2/22 2/23/22	Normal Normal Normal Normal Normal	67 92 90 92 92	11.60 15.15 16.95 15.96 14.74	4.85 7.46 11.92 12.81 11.87	86.2 100.0* 100.0* 95.6 93.5	36.8 50.1 83.4 76.8 75.3	49.4 49.9 16.6 18.9 18.2	6.75 7.69 5.03 3.15 2.87	13.46 14.88 14.03 16.69 15.76	72.8 80.4 77.3 90.2 85.2	36.84 45.54 47.15 51.83 51.30	41.01 50.30 50.52 56.83 56.61	110/80 120/75 130/80 130/80 130/80
11 (1)	Arteriosclerosis, myocardial degeneration, myocardial insufficiency, auricular fibrillation	1/12/22 4/ 1/22	Normal Normal	83 90	17.58 19.96	10.78 12.63	90.5 90.4	55.5 61.0	35.0 35.4	6.80 7.33	19.42 20.79	105.0 111.9	49.00 55.87	56.77 64.00	100/110 100/105
12 (15)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation	11/30/21 12/13/21	Aur. Fib. Aur. Fib.	2 300 c.c. 1,400 c.c.	17.42 18.10	7.31 2.94	88.0 97.6	56.9 15.8	51.1 81.8	10.11 15.16	19.79 18.54	107.0 100.2	48.19 36.06	53.66 46.36	
13 (16)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation	12/22/21	Aur. Fib.	2 800 c.c.	21.23	16.91	94.0	74.8	19.2	4.32	22.58	122.1	39.00	45.00	106 mm.
14 (14)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, cardiac hypertrophy dilatation, myocardial insufficiency, auricular fibrillation	3/ 8/22	Aur. Fib.	48	21.36	16.40	98.1	75.3	22.8	4.96	21.78	117.7	48.73	57.79	120 mm.
15 (17)	Chronic rheumatic endocarditis, pericarditis, mitral stenosis and insufficiency, auricular fibrillation	11/11/21 11/18/21	Aur. Fib. Aur. Fib.	47 37	....	4.35 1.77† 7.35	....	26.6 9.6 40.0	....	....	16.38 18.39	88.54 99.40	....	35.34 56.10† 53.76	95 mm. 130 mm.

* Difference between oxygen content and oxygen capacity is probably due to excess oxygen in physical solution. These were checked by saturating a second sample of blood.

† Deep vein punctured in attempt to get arterial blood. Recorded as of interest, showing difference in saturation between blood from a very deep vein at the elbow and the superficial vein at bend of elbow.

TABLE 4.—Cases in Groups II and III

Case No.	Date	Pulse		Respiration		Artery Used	Digitalis	Quinidin Sulphate	Remarks
		Arterial Puncture	Venous Puncture	Arterial Puncture	Venous Puncture				
10 (6)	1/ 5/22	76	80	18	22	Brachial	0	.....	Slight cyanosis
	1/10/22	66	68	21	21	Brachial	.....	5.4 gm.	No cyanosis
	1/17/22	76	72	18	19	Radial	.....	.....	Subjective improvement
	2/ 2/22	78	72	16	18	Brachial			
	2/23/22	74	74	22	22	Right brachial			
11 (1)	1/12/22	56	54	20	18	Brachial	8-22 to 9-19, 47 c.c.	9-20 to 9-23, 1.6 gm.	No signs cardiac failure. Cardiac reserve good
	4/ 1/22	60	68	20	18	Brachial	9-23 to 10-8, 90 c.c.	5.4 gm.	
12 (15)	11/30/21	66	72	26	24	Brachial	.....	16.0 gm. in two attempts	Cyanosis. No râles. No edema
	12/13/21	62	60	16	18	Brachial	48 c.c.	.....	Few râles at both bases
13 (16)	12/22/21	48	52	24	28	Brachial	52 c.c. in two courses	31.6 gm. in two trials	Cyanosis of lips. Râles at bases
14 (14)	3/ 8/22	64	66	20	22	Right radial	12 c.c.	6.2 gm.	No cyanosis
15 (17)	11/11/21	..	98	..	28	.....	+	0	Cyanosis, râles. No edema
			56	..	21	.....	.....	.....	Dyspnea

He was in the hospital for three weeks and was found to have fibrillation. He was treated with digitalis. He was discharged without signs of failure. In February, 1921, he had a second attack of cardiac failure and was in the hospital for four weeks, following which he was kept on digitalis.

Examination.—There were no signs of cardiac failure, except a slight cyanosis. The heart was slightly enlarged. The rhythm was totally irregular. A loud blowing systolic murmur was heard at the apex, and a systolic murmur over the pulmonic area. This murmur was transmitted to the neck vessels.

Diagnosis.—Chronic rheumatic endocarditis; mitral stenosis; mitral insufficiency; cardiac hypertrophy and dilatation; slight myocardial insufficiency; auricular fibrillation.

Treatment.—Digitalis was not necessary. January 3 the use of quinidin sulphate was begun and the patient reverted to normal mechanism January 4. He was discharged with normal mechanism. Patient still had a normal rhythm when seen in March, 1922.

This patient had two very severe cardiac breaks, and had very little cardiac reserve, but with the continuance of the normal mechanism this was greatly improved. Unfortunately, no blood studies were made during the period of fibrillation. After the onset of the normal mechanism the arterial saturation was low, later going up to a normal level where it remained. There was a venous anoxemia at first but subsequent examinations after the continuance of the normal mechanism showed a great improvement both in the venous saturation and in the coefficient of utilization. The patient's anemia improved and there was marked increase in the vital capacity.

Case 11 (1) (Tables 3 and 4).—Patient, a male, white, aged 49 years, was admitted Aug. 23, 1921, and discharged Oct. 29, 1921, improved, and with normal mechanism.

History.—Precordial pain began in April, 1921. Later, there was dyspnea on exertion and the patient went to a hospital for six weeks. Soon after discharge he began to have abdominal pain and edema of the ankles. When he was admitted here he was complaining of shortness of breath, pain in the stomach and swelling of the feet.

Examination.—He had some dyspnea, râles at bases of the lungs and edema. The cardiac rhythm was totally irregular. The heart was enlarged but there were no murmurs. The liver was enlarged. The Wassermann test was negative. The apex rate was 120, with a pulse deficit of 10. The peripheral arteries were tortuous and thickened.

Diagnosis.—Arteriosclerosis; myocardial degeneration; myocardial insufficiency; auricular fibrillation.

Treatment.—From August 23 to Oct. 8, 1921, the patient received digitalis, but showed only moderate improvement. October 8 the use of quinidin sulphate was begun and the patient reverted to normal mechanism October 10. He was discharged with a normal mechanism.

The patient showed marked myocardial change with a very slight cardiac reserve. Digitalis cleared up his signs of cardiac failure, but as soon as the patient got up the signs returned. With the normal mechanism there was a great subjective improvement, and the building up of the patient's cardiac reserve was very rapid. He was able to

start moderate work again without discomfort. The normal mechanism has persisted for eight months. The blood gas studies were not in progress when the patient reverted to the normal mechanism but subsequent examinations showed, first, an arterial anoxemia which later disappeared and an increased venous saturation, without any change in the coefficient of utilization because of the rise in arterial saturation. The vital capacity increased progressively.

GROUP III

CASE 12 (15) (Tables 3 and 4).—Patient, male, white, aged 45 years, was admitted Nov. 28, 1921, and discharged Dec. 21, 1921, improved, but with auricular fibrillation.

History.—The patient first had dyspnea eighteen years ago. The pulse was irregular in June, 1913. The first cardiac failure was in November, 1920, during an attack of bronchopneumonia. He had two subsequent attacks of cardiac failure. He has taken digitalis since April, 1921.

Examination.—There was slight dyspnea, but no edema, no râles, and no pulse deficit. The rate was 88. The heart was not enlarged. The rhythm was totally irregular. There was a rumbling murmur throughout diastole ending a little before the first sound. The Wassermann test was negative.

Diagnosis.—Chronic rheumatic endocarditis; mitral stenosis and insufficiency; myocardial insufficiency; auricular fibrillation.

Treatment.—Digitalis was not necessary. December 3 the use of quinidin sulphate was started, and was discontinued December 10 because of subjective discomfort. Quinidin was given December 11 but again discontinued because of signs of cardiac failure. December 12 the use of digitalis was started again. The patient was discharged with auricular fibrillation.

The patient showed marked structural change in the heart with greatly diminished cardiac reserve. Attempts to restore the normal mechanism with quinidin sulphate failed and signs of cardiac failure appeared rapidly when digitalis was stopped. The arterial saturation was normal in spite of the pulmonary congestion. There was a marked venous anoxemia, and a high coefficient of utilization, pointing to a very sluggish circulation. This may have accounted for the high arterial saturation, because with the slow blood flow the blood had time to become fully oxygenated in the lung capillaries. The patient was finally discharged with auricular fibrillation, fairly well compensated but with a low cardiac reserve.

CASE 13 (16) (Tables 3 and 4).—Patient, a male, white, aged 39 years, was admitted Dec. 21, 1921, and discharged Jan. 26, 1922, improved, but with auricular fibrillation.

History.—In August, 1919, the patient became dizzy, fainted and vomited. After this he had frequent attacks of indigestion. Dyspnea has gradually come on since then and is the chief complaint at the present time. Patient is now orthopneic.

Examination.—There was dyspnea, slight cyanosis of the lips and fingers, râles at the bases of the lungs posteriorly. The rhythm was totally irregular, with a short systolic murmur at the apex. The second sound was followed after an interval by a soft blowing diminuendo murmur. There was no pulse deficit.

Diagnosis.—Chronic rheumatic endocarditis; mitral stenosis and insufficiency; myocardial insufficiency; auricular fibrillation.

Treatment.—Digitalis was not necessary. December 23 the use of quinidin sulphate was started but discontinued December 30 because of diarrhea. From Jan. 1 to 8, 1922, digitalis was given. January 9 quinidin sulphate was given again. January 19 quinidin was discontinued because of the return of cardiac failure and digitalis was given again. The patient was discharged fibrillating.

This patient was admitted with a mild degree of heart failure but with very little cardiac reserve. Two trials were made with quinidin sulphate without changing the rhythm. As soon as digitalis was stopped, signs of cardiac failure developed at once. Arterial and venous samples taken once during fibrillation showed a very slight anoxic anoxemia with a normal venous saturation and a normal coefficient of utilization.

Case 14 (Tables 3 and 4).—Patient, a female, white, aged 22 years, was admitted March 3, 1922, and died March 12, 1922.

History.—She had had repeated attacks of tonsillitis. The tonsils were excised. An attack of rheumatic fever and the first cardiac break came in 1911. Two subsequent attacks of cardiac failure, with discovery of fibrillation, occurred in June, 1920. She has been fairly comfortable with the use of digitalis since the last attack but becomes very dyspneic and has palpitation on exertion.

Examination.—The heart was enlarged. At the apex there was a blowing systolic murmur, and rumbling middiastolic murmur. The rhythm was totally irregular. The apex rate was 92, the radial pulse was 84. There were no râles and no cyanosis, but there was a slight edema of the ankles. The Wassermann test negative.

Diagnosis.—Chronic rheumatic endocarditis; mitral stenosis and insufficiency; cardiac hypertrophy and dilatation; myocardial insufficiency; auricular fibrillation.

Treatment.—From March 3 to 8, 1922, digitalis was given. March 6, the use of quinidin sulphate was begun and patient reverted to normal mechanism March 11. During the day she was comfortable; at 7:30 p. m., she complained of palpitation and orthopnea. The apex rate was 120; the radial pulse was 60, a typical two to one rhythm. At 2 a. m., March 12, the patient had a short convulsion and died. A necropsy was not permitted but it was supposed that she had cerebral embolism. This was the only fatality directly attributable to the use of quinidin in the series reported in this paper.

This patient showed marked structural cardiac changes with a great functional impairment of the heart. The circulation was quite efficient when the patient was at rest, as shown by the normal arterial and venous saturation. The coefficient of utilization was normal. The vital capacity, however, was greatly diminished. The patient died shortly after the onset of the normal mechanism so that studies were not made on the blood gases after reversion to the normal rhythm.

Case 15 (17) (Tables 3 and 4).—Patient, female, colored, aged 22 years, was admitted Nov. 9, 1921, and died Nov. 28, 1921.

History.—She had had rheumatic fever at 11 years; "dropsy" at 15 years, during a cardiac failure lasting ten months. An attack of influenza in 1918 was followed by cardiac failure. She had pneumonia in March, 1921, which was

followed by the present attack of cardiac failure. Edema and dyspnea, which had occurred only during the menses, now became permanent. She had occasional orthopnea.

Examination.—There were râles at the bases of the lungs. The heart was greatly enlarged. The rhythm was totally irregular. At times a thrill, apparently systolic, was felt in the anterior axillary line in the fifth and sixth interspaces. There was a systolic thrill in the second interspace, in the region of the conus, with systolic and diastolic murmurs at the apex, and a systolic murmur in the second interspace to the left of the sternal line, with marked accentuation of the first and second sounds. The liver was almost down to the umbilicus. It was tender and pulsating. Edema of ankles was present. The Wassermann test was negative.

Diagnosis.—Chronic endocarditis; pericarditis; mitral stenosis and insufficiency; myocardial insufficiency; auricular fibrillation.

Treatment.—From November 11 to 18 the patient received digitalis, when it was discontinued because of nausea and vomiting. November 23 the use of digitalis was started again. The patient steadily grew worse and died.

This is a case of rheumatic heart disease with extreme structural change in the heart, and functionally marked limitation of cardiac reserve. The peripheral circulation was sluggish, as shown by the marked stagnant anoxemia. A deep vein was punctured November 18 in an attempt to do an arterial puncture. The blood taken from this vein was much less saturated than that taken from the median basilic vein. No further attempt was made to do an arterial puncture because of the patient's condition. There was an increase in oxygen capacity between the two punctures pointing to a failing circulation with an attempt to overcome the failure by an increase in hemoglobin.

DISCUSSION

In seven out of the nine cases studied during fibrillation and during the normal mechanism there was an increase in the venous oxygen saturation and a decrease in the coefficient of utilization under the normal mechanism. The term coefficient of utilization of oxygen carrying power of the blood was introduced by Krogh and Linhard [17] and was emphasized by Means and Newburgh.[18] This term is applied to the difference between the arterial and venous oxygen saturation in terms of percentages. It is normally below 30 per cent., with an average arterial saturation of 95 per cent. and a venous saturation of 65 per cent. or more. It may be pointed out that with an arterial saturation of 85 per cent. and a venous saturation of 55 per cent. the coefficient of utilization remains 30 per cent., and from the point of view of the systemic blood flow the circulation is just as efficient as in the first case, the respiratory exchange of the blood taking place on a lower level. Cyanosis occurs at a higher figure of oxygen saturation when an anoxic anoxemia is present as well as a stagnant anoxemia,

17. Krogh, A., and Linhard, J.: Skand. Arch. f. Physiol. **27**:100, 1912.
18. Means, J. H., and Newburgh, L. H.: Tr. Assn. Am. Phys. **30**:51, 1915.

than it does in the presence of a normal arterial saturation. Lundsgaard [19] suggested this by indirect figures, and Stadie [6] by taking arterial samples proved it to be the case in pneumonia.

The improvement in the venous saturation and the decrease in the coefficient of utilization we have interpreted as due to an improvement in the systemic blood flow; if the circulation rate is increased the blood does not remain in the capillaries as long and the blood entering the veins has not given up as much oxygen to the tissues as is the case at a slower rate. If, in response to the need of the tissues, a definite volume of oxygen leaves a unit volume of blood in a given time, when twice the volume of blood passes through the same area and the same amount of oxygen is extracted, each unit volume of blood will give up only one half the volume of oxygen previously lost, and the venous oxygen saturation will, therefore, be so much the higher. The ability of the tissues to use oxygen at a very low tension is seen in anemia where the blood leaving the capillaries may be almost completely deprived of oxygen.[19] Meakins [20] showed that when an area is exposed to cold, venous blood may contain little or no oxygen. It hardly seems possible that a change in tissue metabolism, or in the cross section of the capillary bed would so constantly take place with the onset of the normal mechanism as to give the increased venous saturation, and it seems much more likely that the change is due to an improved blood flow.

All the cases, except Case 1, showed a decrease in the percentage of arterial saturation immediately after the onset of the normal mechanism. The arterial saturation returned to normal in all cases except two in which there was a pathologic lesion (emphysema) which would tend to prevent it. In Case 7, although the respiratory minute volume was increased after the onset of the normal mechanism, and the vital capacity was also increased, nevertheless, the arterial saturation was decreased immediately after the onset of the normal mechanism in spite of the improved pulmonary ventilation. We have explained this phenomenon in the following way. During fibrillation the blood flow through the lung capillaries is slow, and the blood has time to reach a maximum oxygenation. With the onset of normal mechanism and the more rapid circulation rate, the blood does not stay in the lung capillaries so long, and does not have time to reach the maximum saturation with oxygen. Later there is a compensation for this and the blood becomes fully saturated.

In seven of the nine cases in Group I there was a diminution in oxygen consumption after the onset of the normal mechanism and Case 2 showed it with each reversion to the normal rhythm. Cases

19. Lundsgaard, C.: J. Exper. M. **30**:271, 1919.
20. Meakins, J. C.: J. Path. & Bacteriol. **24**:79, 1921.

2, 6 and 7, with high oxygen capacities, and Cases 1 and 3 with slightly lower oxygen capacities, showed a decrease in oxygen capacity after the onset of the normal mechanism or with its continuance. It would seem that the high hemoglobin content in these cases was a response to oxygen want during fibrillation, and was a compensatory mechanism. The chronic cardiac as well as the chronic pulmonary emphysema patient very often has a high oxygen capacity, which must be looked on as one of the mechanisms of the body to make up for the impaired circulation in the one case and the incomplete oxygenation of the blood in the lungs in the other, and when fibrillation is added to either condition there is an increased loss of efficiency.

Case 4 with a marked anemia improved greatly after the onset of the normal rhythm. How much of the later improvement was due to iron in the form of Blaud's pill cannot be estimated. Five other cases with moderate anemia or normal hemoglobin had an increase in the oxygen capacity with the normal mechanism.

The behavior of the carbon dioxid content of the arterial and venous blood was variable. Case 1 had a low carbon dioxid content after the onset of the normal mechanism which gradually rose to normal. Case 2 also had a low carbon dioxid content which increased with the normal rhythm and continued to increase when the patient later reverted to fibrillation. Case 3 had a carbon dioxid content at the normal level during fibrillation which decreased with the normal rhythm, later slowly rising to normal. Case 4 with a low carbon dioxid content during fibrillation had a further decrease after the normal mechanism but this later went above normal. The carbon dioxid content of the venous blood in Case 6 on one analysis was 68.55 volumes per cent. at a time when the patient was near an open window, and was feeling chilly and had marked cyanosis. Case 7 showed the high carbon dioxid content which has been found in chronic pulmonary emphysema. There was no change after the onset of the normal mechanism. The carbon dioxid capacity of the venous plasma in this case was 78.21 volumes per cent.

All patients, with the exception of Case 9, showed an improvement in the vital capacity after the onset of the normal mechanism, which apparently made possible a more efficient pulmonary ventilation. The disappearance of dyspnea after the onset of the normal mechanism, coincident with improvement in the vital capacity lends weight to the suggestion of Peabody [21] that cardiac dyspnea is due in part to diminished vital capacity.

The details of the quinidin therapy of these patients with a study of their progress from a clinical point of view are given by Burwell

21. Peabody, F. W., and Wentworth, J. A.: Arch. Int. Med. **20**:443 (Sept.) 1917.

and Dieuaide [22] in which the same case numbers are used as in the present paper. These studies show that the circulation is improved by the restoration of the normal mechanism and offer a rational basis for an attempt to bring about reversion to the normal mechanism by the use of quinidin sulphate in selected cases. The advantages of quinidin therapy seem to be four:

1. Marked subjective improvement of the patient under the normal mechanism.

2. Great increase in the cardiac reserve.

3. Improved pulmonary ventilation.

4. Improvement in the oxygen saturation of the venous blood, and on the basis of the coefficient of utilization, improvement in the peripheral systemic blood flow.

SUMMARY

1. Fifteen cases of auricular fibrillation were studied from the poin. of view of the blood gases. Fourteen of the patients received quinidin sulphate; twelve reverted to normal mechanism. One patient died soon after reversion to normal mechanism, so that no studies were made during the normal rhythm. Unfortunately, in two other cases no studies were made in the presence of fibrillation but the progressive improvement with persistence of the normal mechanism is clearly shown. The nine remaining cases were carefully studied during fibrillation and during the normal mechanism.

2. Seven of the nine cases referred to above showed a definite increase in the venous oxygen saturation and a diminution in the coefficient of utilization and in oxygen consumption with the onset of normal mechanism, which was interpreted as due to an improvement in the blood flow. Two other cases showed improvement with continuance of the normal mechanism.

3. A reduction in percentage of the arterial oxygen saturation with the onset of normal mechanism, followed later by an increase in the percentage of arterial oxygen saturation to normal (except in two cases of emphysema), was consistently found. An explanation of this phenomenon is offered.

4. Two cases showed no improvement in the venous oxygen saturation, nevertheless, one of these patients was greatly improved clinically while the other reverted to fibrillation almost immediately.

5. In three cases with a high oxygen capacity and two others with a lower oxygen capacity there was a definite fall in oxygen capacity after the onset of normal mechanism. It is suggested that the high hemoglobin present was a compensatory mechanism.

22. Burwell, C. S., and Dieuaide, F. R.: Arch. Int. Med., to be published.

6. In one case of rather severe anemia there was a marked rise in the hemoglobin under the normal mechanism. Five other patients with moderate anemia or normal hemoglobin showed an improvement in the oxygen capacity with continuance of the normal mechanism.

7. The changes in the carbon dioxid content were variable.

8. The vital capacity was consistently increased after the onset of the normal mechanism.

EXPERIMENTAL URANIUM NEPHRITIS

A CHEMICAL AND PATHOLOGIC STUDY *

FRANKLIN R. NUZUM, M.D.
AND
LEONARD L. ROTHSCHILD, M.D.
SANTA BARBARA, CALIF.

It is well known that uranium nitrate given subcutaneously to laboratory animals will produce varying degrees of kidney injury. Large single doses cause an extremely acute necrosis of the cells lining the convoluted tubules, from which the animal may not recover. But when smaller doses are given over a long period of time, a marked chronic nephritis results. Dickson [1] demonstrated this in guinea-pigs. Christian [2] and his associates have produced it in rabbits. MacNider [3] has obtained similar results in rabbits and dogs.

The kidney pathology in experimental uranium nephritis has been described. The urinary changes during the uranium intoxication have also been followed. But since much of this work was done before the advent of blood chemistry, correlated studies of the chemical changes in the blood and urine, the renal functional tests and the pathology of the kidneys at various stages of the intoxication have not been frequently done. MacNider's researches must be excepted. He has advanced our knowledge of experimental nephritis materially.

The present work was undertaken as a correlated study of the pathology of uranium nephritis and the various chemical changes in the blood and urine. These changes were followed for long periods of time.

Material.—A large number of rabbits were used. They varied from 9 to 12 months in age. None of them had spontaneous nephritis since their blood and urine chemistry was carefully studied before their intoxication with uranium began. Some animals were discarded because they had a spontaneous nephritis.

Method.—Selected animals were placed in separate metabolism cages. Each was fed 100 gm. of a mixed diet of cabbage leaves, barley, carrots and alfalfa hay. They were given water ad libidum. The

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* From the laboratories of the Santa Barbara Cottage Hospital.

1. Dickson, E. C.: A Further Report on the Production of Experimental Chronic Nephritis in Animals by the Administration of Uranium Nitrate, Arch. Int. Med. **9**:557 (May) 1912.

2. Christion, H. A., and O'Hare, J. P.: Glomerular Lesions in Acute Experimental Nephritis, J. Med. Research **23**:227, 1913; Christian, H. A.; Smith, R. N., and Walker, I. C.: Experimental Cardiorenal Disease, Arch. Int. Med. **8**:469 (Oct.) 1911.

3. MacNider, Wm. de B.: A Functional and Pathologic Study of the Chronic Nephropathy Induced in the Dog by Uranium Nitrate. J. Exper. Med. **29**:513, 1919; A Pathologic Study of the Naturally Acquired Chronic Nephropathy of the Dog, J. Med. Research **34**:177, 1916.

urine from each cage was caught in a vessel containing 5 c.c. of a 5 per cent. solution of hydrochloric acid to prevent the conversion of urea into ammonia (NH_3), in the normally alkaline rabbit urine. These specimens were analyzed for albumin, and, if present, the amount in grams was recorded. Casts were searched for in centrifuged specimens.

The total nitrogen (T.N.) of the urine was determined by the simplified Kjeldahl method;[4] the urea nitrogen (U.N.) by the Folin and Youngberg method;[5] the ammonia (NH_3) by the microchemical method of Folin and McCollum;[6] the creatinin (C.N.) by the Folin colorimetric method;[7] the uric acid nitrogen (U.A.N.) by the Folin and Wu method,[8] and the organic acids (O.A.) by the Van Slyke and Palmer methods.[9] Acetone and diacetic acid were also sought for by the usual tests.

Sufficient blood was withdrawn from the marginal ear vein into a flask containing 10 mg. of calcium oxylate to determine the nonprotein nitrogen by the method of Folin and Wu;[10] the urea nitrogen by the method of Folin and Wu;[10] the carbon dioxid by the method of Van Slyke and Cullen,[11] and the alkali reserve ($R\rho_H$) by the method of Marriott.[12]

From twenty-four to forty-eight hours following an initial subcutaneous injection of from 2 to 4 mg. of uranium nitrate dissolved in sterile distilled water, various changes were noted in the blood and urine. The nonprotein nitrogen of the blood, for example, increased daily for from three to six days and then dropped again until approximately a normal level was reached. The animal was then allowed to rest a sufficient time to permit all acute reaction in the kidney to subside. He was then given a larger dose of uranium nitrate subcutaneously and the various tests were repeated. The rest periods between the injections of uranium varied roughly from three to sixty days. The irregularity of this interval was due to the varying time each animal

4. Folin, O. F.: A Simplified Kjeldahl Method for Urine, J. Biol. Chem. **38**:461, 1919.

5. Folin, O. F., and Youngberg, G. E.: Note on the Determination of Urea in Urine by Direct Nesslerization, J. Biol. Chem. **38**:111, 1919.

6. Folin, O. F., and McCollum, A. B.: On the Determination of NH_3 in the Urine, J. Biol. Chem. **2**:523, 1912.

7. Folin, O. F.: Approximately Complete Analyses of Thirty Normal Urines, Am. J. Physiol. **13**:45, 1905.

8. Folin, O. F., and Wu, H.: A Revised Colorimetric Method for the Determination of Uric Acid in Urine, J. Biol. Chem. **38**:459, 1919.

9. Van Slyke, D. D., and Palmer, W. W.: Titration of Organic Acids, Proc. Soc. Exper. Biol. & Med. **16**:140, 1919.

10. Folin, O. F., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

11. Van Slyke, D. D., and Cullen, G. E.: The Bicarbonate Concentration of the Blood Plasma; Its Significance, and Its Determination as a Measure for Acidosis, J. Biol. Chem. **30**:289, 1917.

12. Marriott, W. McK.: A Method for the Determination of the Alkali Reserve of the Blood Plasma, Arch. Int. Med. **17**:840 (June) 1916.

required to reestablish his acid base equilibrium and for his blood and urine chemistry to return as nearly to their normal levels as possible. During the later stages of the experiments, normal figures were not reached because a marked chronic nephritis had been established.

The dosage of uranium per injection was gradually increased from 2 mg. to the notably high figure of 50 mg. The longest and the shortest experiments included in this report covered periods of one hundred and seventy-five and seventy-four days, respectively. Data from animals dying during the earlier days of the experiments are not included in this study.

A statistical table was made for each animal. The various findings for each day were recorded. From these tables curves have been plotted which depict graphically the rise and fall of the chemical constituents of the blood and urine.

With all of this data before us in both table and graphic form, we have noted the various findings in each individual instance and the findings of one rabbit as compared with another. For example, we have compared the organic acids of the urine with the alkali reserve and the carbon dioxid of the blood, since each of these may be used clinically as an index of the acid-base balance. When there is an acidosis, as determined by the above methods, we have studied the ammonia of urine together with its total nitrogen and urea nitrogen. At the same time we have noted the presence and amount of albumin, of casts, of acetone and diacetic acid. Likewise we have studied the nonprotein nitrogen and urea nitrogen of the blood, noting their rise and fall and their relation to the urine findings.

Finally, these animals having given evidence of a chronic nephritis for a long period of time, their phenolsulphonephthalein elimination was determined and they were killed. A careful postmortem examination was made. The kidneys were given especially careful histologic study.

Results.—Following an injection of uranium there occurred, within from twenty-four to forty-eight hours, a decrease in the amount of urine excreted. This was followed by a marked increase, which usually reached a maximum from the fifth to the seventh day and then gradually decreased, reaching an approximate normal from the tenth to the twelfth day.

Urine Chemistry.—Albumin and casts appeared within twenty-four hours following the injection of uranium. They disappeared in a few days following the first and smaller injections, but during the latter part of the experiments albumin was continually present and casts were usually found for some days following each injection. There was, however, no constant relation between the amount of albumin excreted and the chemical findings of either blood or urine, nor with the degree of acidosis present. This also holds true with nephritis in man. It has frequently been demonstrated that the albumin content of the urine

Data from Animal I

Uranium	Day of Experiment	Urine												Blood			
		Amount of Urine	Albumin	Casts	Acetone	Diacetic Acid	Organic Acids	Phenolsulphonephthalein	Total N	Urea N	NH_3	Creatinin	Uric Acid N	Non-protein N	Urea N	R p_H	CO_2
Normal	0	230	0	0	0	0	90.0	88%	0.92	0.65	0	0.13	0.068	38.0	17.4	8.4	59.5
4 mg.	1	80	0	0	0	0	.....	....	0.43	0.30	0	0.081	0.032	39.2	18.2	8.3	51.9
	2	210	0.75	2+	0	0	.....	....	1.18	0.58	0.004	0.13	0.067	48.0	26.0	7.9	37.0
	3	270	1.75	2+	0	0	.....	....	0.71	0.40	.....	0.082	.....	69.2	43.2	8.0	44.9
	4	85	1.50	4+	0	0	.....	....	0.44	0.077	.....	0.043	.....	100.0	64.0	8.05	42.1
	5	85	1.20	2+	0	0	.....	....	0.43	0.12	0.009	0.050	0.006	133.0	88.0	8.25	52.0
	6	180	1.50	2+	Trace	0	.....	....	0.68	0.50	0.0016	0.054	0.008	182.0	113.0	8.25	48.0
	7	140	0.75	0	0	0	.....	....	0.53	0.24	Trace	0.042	0.008	137.0	88.0	8.2	48.9
	8	130	0.80	0	0	0	.....	....	1.15	0.63	0	0.12	0.009	98.0	66.5	8.3	52.4
	9	175	0.50	0	0	0	.....	....	1.57	1.19	0	0.15	0.025	50.0	33.4	8.3	49.9
	10	165	0	0	0	0	.....	....	1.50	1.16	0	0.11	0.024	34.0	22.2	8.3	50.2
	11	140	0	0	0	0	.....	....	0.73	0.53	0	0.16	0.027	.....	....	...	....
4.5 mg.	44																
	45	190	0	0	0	0	118.4	....	1.94	1.82	0	0.1	0.022	66.8	42.0	8.35	51.9
	46	450	1.75	2+	0	0	.....	....	2.39	1.95	0.008	0.1	0.031	105.0	67.5	8.35	55.6
	47	220	1.00	4+	0	0	114.4	....	1.05	0.87	0.044	0.066	0.005	105.0	90.0	8.3	59.5
	48	250	0.5	1+	0	0	120.0	....	1.29	1.02	0.004	0.063	0.009	152.0	122.0	8.4	63.1
	49	140	0	0	0	0	157.0	....	0.74	0.63	Trace	0.032	0.003	150.0	126.0	8.3	50.2
8 mg.	100																
	101	340	0.5	1+	0	0	258.0	....	1.82	1.59	0.014	0.14	0.031	65.0	41.0	8.3	53.0
	102	155	2.0	4+	0	0	102.0	....	0.87	0.66	0.008	0.062	0.005	62.5	42.5	8.4	55.7
	103	220	2.0	4+	0	0	167.0	....	1.54	1.13	0.001	0.10	0.006	60.0	38.0	8.1	45.5
	104	250	1.0	4+	+	0	160.0	....	1.62	1.35	0.009	0.13	0.008	63.5	47.5	8.1	46.2
	105	500	1.0	0	0	0	380.0	....	2.10	1.74	0.14	0.10	0.014	68.0	42.0	8.1	43.0
12 mg.	107																
	108	340	0.25	+	0	0	326.0	....	0.84	0.45	0.002	0.12	0.017	58.0	27.5	8.1	40.4
	109	510	0.5	1+	0	0	285.0	....	1.74	1.39	0.029	0.13	0.026	50.0	22.5	8.1	42.4
	110	340	0.75	2+	0	0	218.0	....	0.58	0.42	0.027	0.075	0.023	50.0	24.6	8.1	42.5
	111	335	0.75	2+	0	0	204.0	....	0.95	0.75	0.024	0.15	0.02	53.5	27.8	8.0	38.6
	112	300	0.75	2+	0	0	144.0	18%	0.69	0.50	0.02	0.09	0.027	60.0	40.0	7.8	29.4
30 mg.	134																
	135																
	136	300	1.5	4+	+	+	288.0	....	0.84	0.41	0.026	0.075	0.02	50.0	27.0	8.1	47.8
	137	410	1.0	3+	0	0	328.0	....	0.86	0.48	0.03	0.066	0.018	48.0	24.5	8.1	44.6
	138	200	1.5	1+	Trace	0	208.0	....	0.78	0.46	0.023	0.044	0.008	52.0	25.0	8.35	55.7
	139	340	1.5	0	0	0	501.0	....	0.95	0.56	0.07	0.039	0.02	53.5	26.0	8.3	51.0
	140	360	1.0	0	0	0	360.0	....	0.91	0.62	0.042	0.05	0.018	45.0	26.5	8.1	46.2
40 mg.	141																
	142																
	143	470	1.0	2+	0	0	132.0	....	1.15	0.95	0.027	0.047	0.017	63.0	41.0	8.3	53.0
	144	510	1.0	+	0	0	.....	....	1.39	1.17	0.044	0.064	0.014	84.0	50.0	8.3	54.0
	145	400	1.0	2+	0	0	224.0	10%	1.35	1.13	0.018	0.1	0.026	75.6	51.5	8.2	52.1
	146	450	0.5	+	0	0	.....	....	0.95	0.38	0.05	0.05	0.005	125.0	107.0	7.9	35.0
	147	300	0.5	+	0	0	.....	....	1.40	1.16	0.06	0.06	0.03	200.0	160.0	7.9	34.2
	148*																

* Animal died. Pathology of kidney; mixed acute and chronic change.

is not an index of the functional ability of the kidney nor of the extent of the kidney damage present.[13]

The total nitrogen and the urea nitrogen of the urine bore a fairly constant relationship to each other throughout these experiments. Immediately following the injection of uranium both decreased in amount. From the second to the fourth day they began to increase,

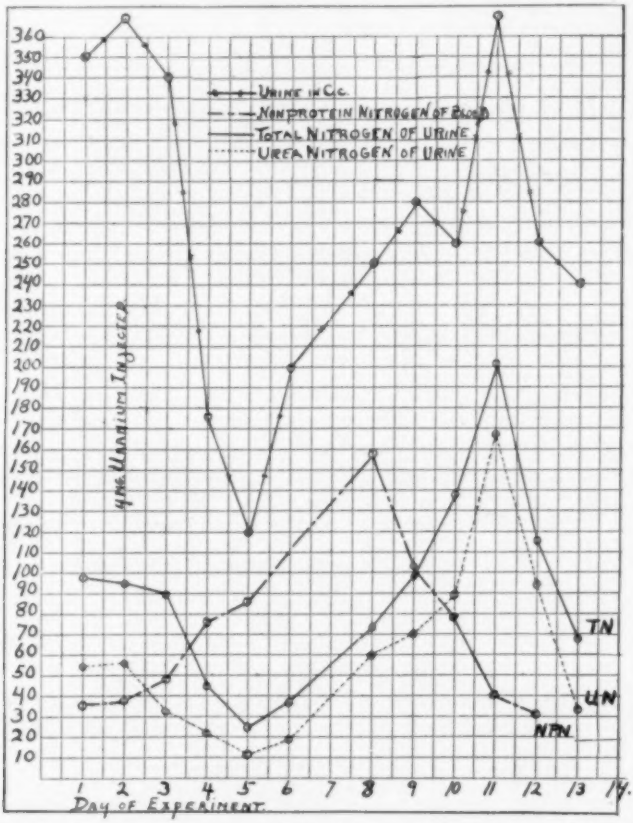

Fig. 1.—Changes in the nonprotein nitrogen of the blood and in the total nitrogen, urea nitrogen and the amount of urine following an injection of 4 mg. of uranium in Rabbit 5.

reaching a maximum amount in the urine two or three days after the nonprotein nitrogen in the blood was highest, then gradually returning to normal (Fig. 1). The total nitrogen of the urine was frequently

13. Moschowitz, E.: Clinical and Anatomic Relations in Chronic Nephritis, Arch. Int. Med. **24**:259 (Aug.) 1920.

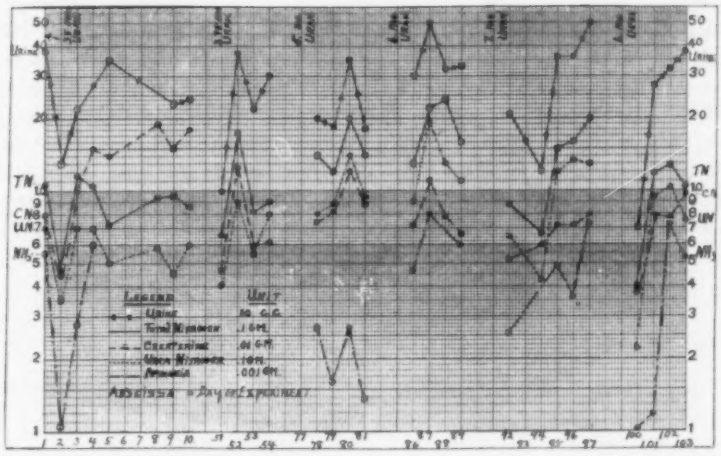

Fig. 2.—Illustrating the marked similarity in the variation of the amounts of the total nitrogen, urea nitrogen, ammonia, organic acids and the total urine, following repeated injections of uranium, when charted on logarithmic paper (Rabbit 4).

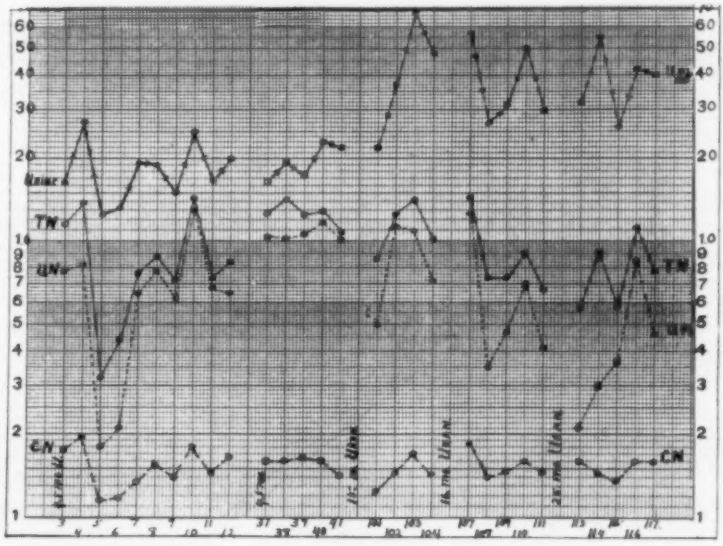

Fig. 3.—The same curves as in Figure 2 when plotted from data obtained from Rabbit 6.

increased to twice its normal amount. The highest reading obtained was 3.34 gm. in a twenty-four hour specimen of urine of which the normal reading was 1.15 gm. The urea nitrogen in this same experiment and on the same day was 3.15 gm. in a twenty-four hour specimen of urine, whereas its normal level was 0.92 gm. The curves representing the increase and decrease in the amounts of total nitrogen, urea nitrogen, the organic acids and ammonia in the urine and the curve representing the total amount of urine were quite uniformly proportionate when plotted on logarithm paper (Figs. 2, 3, and 4). These changes were uniform enough so that by following two of these urinary constituents a fair idea of the kidney activity was obtained.

Traces of acetone and diacetic acid were present in the urine following the initial doses of uranium nitrate in only two rabbits. Following

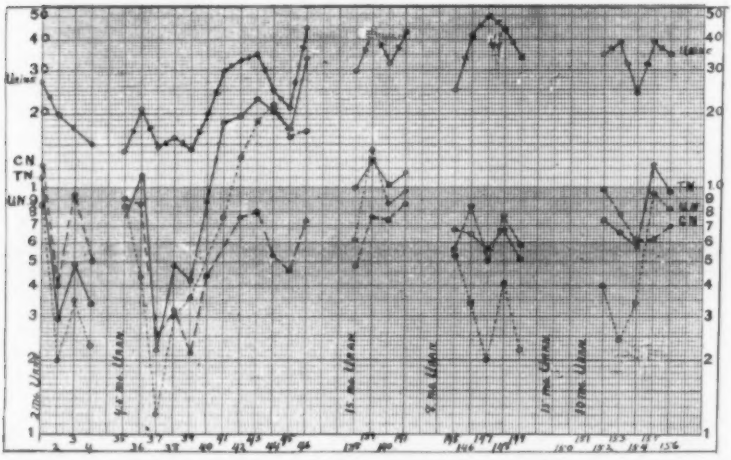

Fig. 4.—The same curves as in Figure 2 when plotted from data obtained from Rabbit 3.

the larger doses they were quite regularly present in amounts varying from a trace to three plus. In one instance, however, following an injection of 40 mg. of uranium nitrate, as a result of which the carbon dioxid of the blood serum ranged from 25.5 to 33 volume per cent. and the alkali reserve fell as low as 7.6, there occurred no trace of either acetone or diacetic acid. This is not in accord with the belief of MacNider that the toxicity of uranium is dependent on its ability to produce organic acids and acetone bodies.[14]

14. MacNider, Wm. de B.: The Inhibition of the Toxic Effect of Uranium Nitrate by Sodium Carbonate and the Protection of the Kidney Acutely Nephropathic from Uranium from the Toxic Action of an Anesthetic by Sodium Carbonate, J. Exper. M. **23**:171, 1916.

The creatinin and urea acid nitrogen of the urine showed less gross deviation from the normal than any of the constituents studied. But when the changes were charted on logarithm paper they were found to be proportionately as marked as any of the other constituents. However, in one animal (Rabbit 3), both were slightly decreased throughout the entire experiment which ran 175 days. At the end of this experiment the phenolsulphonephthalein output was reduced to 10 per cent. in two hours. Pathologically, these kidneys presented the most marked chronic change of any of the series, as is shown in the pathological report.

Blood Chemistry.—Following the initial injection of uranium nitrate, each animal reacted with a sharp rise in the nonprotein nitrogen and the urea nitrogen of the blood. These increased amounts reached a maximum from the fourth to the seventh day and then gradually

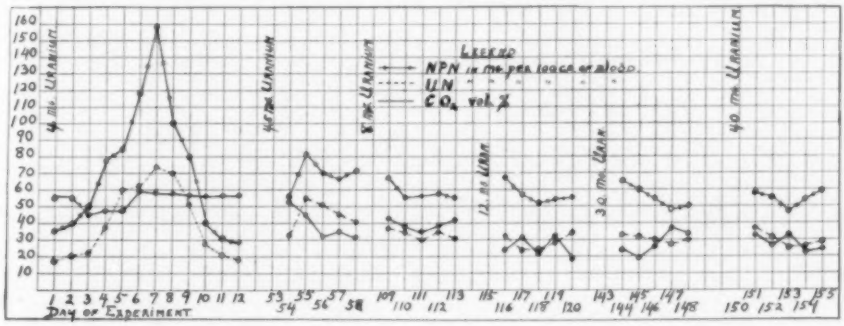

Fig. 5.—The changes of the nonprotein nitrogen, the urea nitrogen and the carbon dioxid of the blood following repeated injections of uranium (Rabbit 5). The similarity of the curves of the nonprotein nitrogen and the urea nitrogen is apparent. The continued disturbance of the acid-base balance is shown by the curve of the carbon dioxid of the blood serum.

receded. The highest figures obtained were 301 mg. nonprotein nitrogen and 215 mg. urea nitrogen per hundred cubic centimeters of blood and followed an injection of 4.5 mg. uranium nitrate in a rabbit weighing 7 pounds. Following the second injection in each of the animals, the rise of the nonprotein nitrogen and of the urea nitrogen was not so pronounced. Succeeding injections, although the amount of uranium became as high as 50 mg., often resulted in a comparatively small increase in these constituents (Fig. 5). However, during all of this time a chronic nephritis was present and the nonprotein nitrogen and the urea nitrogen had reached and maintained a level much higher than normal.

Acid Base Equilibrium.—As a contrast to the changes in the nonprotein nitrogen and the urea nitrogen readings, the disturbance of the acid-base equilibrium became more marked following each injection (Fig. 6). In some unpublished work we have found, as had MacNider,[15] that readings of the carbon dioxid and alkali reserve begin to fall at about the twelfth hour following the injection of uranium, and that the curves continued downward from this time. The disturbance of the acid-base balance seems to precede any other change in either the blood or urine. It also appears to precede any histologic change in the kidney or the liver, excepting, possibly, an increased amount of fat in certain of the liver and kidney cells. In the liver the cells about the periphery of the lobule show an apparent increase in the amount of stainable lipoid material eighteen hours following the uranium injection. In the cells lining the loops of Henle and the convoluted tubules of the kidney there is, likewise, an increase in the amount of stainable lipoid

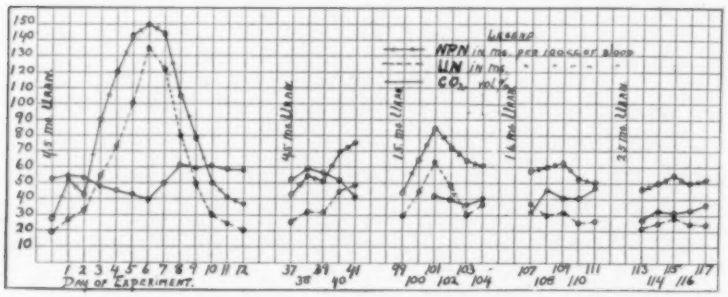

Fig. 6.—Curves illustrating the same changes as in Figure 5, obtained from data from Rabbit 6.

at this time. When the total fat in the liver is extracted with ether in a Soxhlett apparatus, we have found a definite increase as compared with the amount of fat in control rabbit livers. Likewise, we have found the total fat of the kidney to have increased within eighteen hours following the uranium intoxication. This increase in the total amount of fat continues up to forty-eight or even seventy-two hours, apparently reaching a maximum within seventy-two hours.

In rabbits that die following a single injection of uranium, the carbon dioxid and the alkali reserve reach low figures and the excretory functions of the kidney are practically suspended. The organic acids of the urine in one such instance increased from 90 degrees in twenty-four hours to 426 degrees in twenty-four hours, during the last few

15. MacNider, Wm. de B.: Concerning the Amount of Distribution of Stainable Lipoid Material in Renal Epithelium in Normal and Acutely Nephropathic Animals, with Observations on the Functional Response of the Kidney, Proc. Soc. Exper. Biol. & Med. **11**: 1922.

days of life, while the ammonia increased from 0.003 gm. to 0.053 gm. and the creatinin from 0.039 gm. to 0.099 gm. in the twenty-four hour specimens of urine. The statement has been made that the ammonia does not increase in the urine in patients with chronic nephritis associated with acidosis.[16] This statement does not hold for experimental uranium nephritis in rabbits. The increase of creatinin in the urine is an expression of the kidney effort to excrete this substance which is accumulating in the blood. Its accumulation in the blood has proved of dependable prognostic value.

When a chronic nephritis had resulted from repeated injections of uranium, a persistent acidosis was established in all of our animals. In one instance the carbon dioxid never became higher than 35 volumes per cent. from the one hundred and sixteenth to the one hundred and

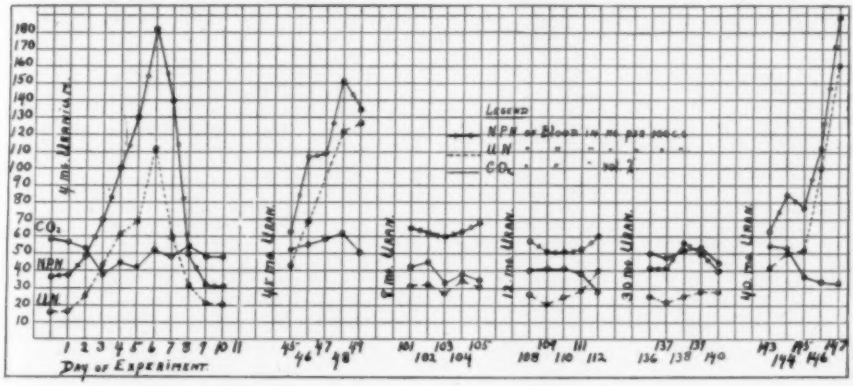

Fig. 7.—Curves similar to those of Figure 6 obtained from data on Rabbit 1. In this single instance there was a marked increase in the nonprotein nitrogen and the urea nitrogen following the final injection of uranium on the one hundred and forty-third day.

fifty-fifth day of the experiment, at which time the animal was killed (Rabbit 5). During this time the organic acids of the urine ranged from 216 to 480 degrees.

The ammonia of the urine was little altered as a result of the milder intoxications, but during the latter course of the experiments it was increased from ten to forty times with a maximum increase of eighty times.

The organic acids of the urine were followed throughout these experiments to see how accurate an index this method gave as to the

16. Marriott, W. McK. and Howland, J.: The Influence of Acid Phosphates on the Elimination of Ammonia in the Urine, Arch. Int. Med. **22**:477 (Oct.) 1918.

degree of acidosis. Normal readings in nonnephritic rabbit urines varied from 90 to 120 degrees acidity. Whenever an acidosis was present, as evidenced by the alkali reserve and carbon dioxid readings, there was an increase in the organic acids. This increase was most marked at the time of greatest acidosis. But the total amount of acids seemed to bear a more uniform relation to the total amount of urine (Fig. 8), and did not follow the alkali reserve and carbon dioxid readings closely enough to make this test as dependable as the latter. The

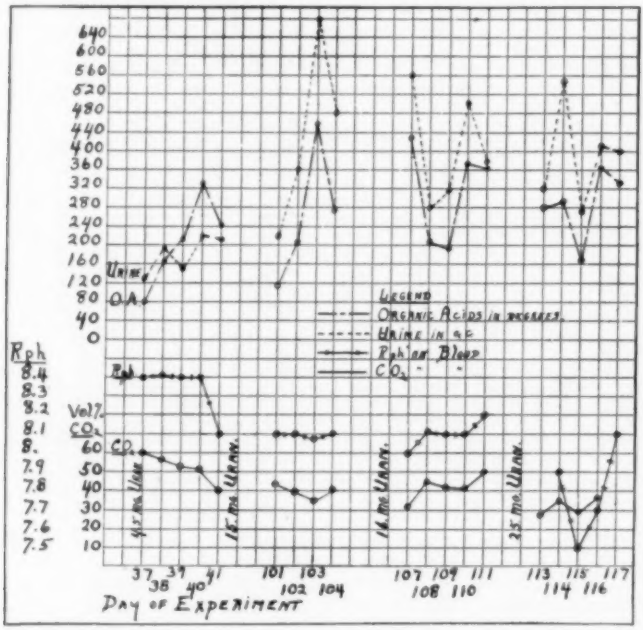

Fig. 8.—Illustrating the similarity of the curves representing the total amount of the urine to the organic acids of the urine. The relationship of the curves of the alkali reserve to the carbon dioxid of the blood serum is also shown (Rabbit 6).

ease of doing the organic acid test as compared with the technic of the alkali reserve and carbon dioxid would tend to make the former a more popular method, provided it gave as accurate results.

Pathology.—The gross changes were limited to the kidneys. When an animal died of a single dose of uranium, the kidneys were enlarged and of a pale color. The capsule stripped easily, leaving a smooth surface. The cut surface bulged. The cortex was increased in width and its markings were indistinct.

The kidneys from animals that were killed after having received many doses of uranium were not enlarged. The capsule usually stripped with some difficulty, leaving a slightly rough surface. On cut section no notable change was observed. The microscopic findings were much more marked.

PROTOCOL OF EXPERIMENTS

RABBIT 1.—This animal had received a total of 98.5 mg. of uranium over a period of 147 days and was killed six days following the last dose of 40 mg. The sections have a patchy appearance. The tubules which were damaged early in the experiment are lined with rows of low cells with irregular nuclei which often push the inner edge of the cell into the lumen of the tubule. The lumen of the tubule in such instances is increased in width. Adjacent to this group are tubules with cells so swollen that the lumen is entirely filled. There are hyaline casts in many of the collecting tubules. Between the cortex and medulla, especially about the blood vessels, fibroblasts are numerous. On the whole, however, there is little connective tissue increase. The glomerulae are not altered.

Summary: Mixed, acute and chronic degenerative changes.

RABBIT 2.—A total of 31 mg. of uranium was injected over a period of seventy-four days. Throughout the entire cortex are scattered many round cells. There is an increased cellularity of the glomerular tufts. The endothelial cells lining the tuft capillaries are swollen so that the lumen of the capillaries is compressed and contains less blood than usual. There is an exudate between Bowman's capsule and the tuft. The cells of the convoluted tubules are swollen so that the lumen is filled. The nuclei stain poorly and the cell cytoplasm has a milky, pale, structureless appearance.

Summary: Acute degenerative changes involving the convoluted tubules and the glomerulae.

RABBIT 3.—In this case 50.5 mg. of uranium were given over a period of 175 days. The tubules are dilated and are lined by low epithelial cells. They frequently contain hyaline casts. The cytoplasm of these cells is granular and the nuclei are irregular in shape and size and occupy various positions in the cell. There is a sharp infiltration of round cells especially about some of the glomerulae and along the limbs of Henle. The round cells are epithelioid in character, with large nuclei. There are also some leukocytes. There is also a round cell infiltration of a lesser degree about some of the collecting tubules. The glomeruli are crowded together in many instances and vary markedly in size. Bowman's capsule is thickened in some instances. There is an increase of fibroblasts in the tuft so that it is more cellular than normal. There is an actual increase of fibrous connective tissue throughout the cortex. These kidneys present, then, a marked increase in fibrous connective tissue, atrophy of some tubules, dilatation of others and chronic cellular change in others. This is an excellent example of chronic change.

RABBIT 4.—This animal received, over a period of 103 days, a total of 81 mg. of uranium, 50 mg. having been given two days before death. These kidneys present an extreme, acute degeneration. The cells lining the convoluted tubules and the ascending and descending loops of Henle are so swollen that the entire tubules are filled, the cell outlines are obliterated and the nuclei themselves are for the most part not visible. These changes are so evident that patches of the section appear solid gray; the glomerulae in these portions being surrounded by such filled up patches. The glomeruli contain fine hyaline-like bodies in the capillary walls (Councilman's bodies). This is the only instance in which these bodies are found.

The tubules in the outer portion of the cortex are much less involved, although their lumens are filled with necrotic material and the cells themselves are less well defined than usual.

Summary: Extreme, acute degenerative changes in the tubules with hyaline droplets in the glomerular tufts.

RABBIT 5.—Over a period of 155 days 98.5 mg. of uranium were injected. The convoluted tubules and the loops of Henle present evidence of moderate chronic change. Low irregular cells line the tubules. There are many hyaline casts in the tubules. There are scattered areas of round cell infiltration representing beginning fibrosis. There is a proliferation of the capillary epithelium with less blood than usual in the tufts. There is also a slight thickening of Bowman's membrane.

Summary: Moderate chronic change.

RABBIT 6.—The total amount of uranium injected over a period of 136 days was 65 mg. The convoluted tubules have, for the most part, undergone chronic changes, as heretofore described. The cells lining the tubules are lower than normal. The nuclei take up a proportionately larger amount of space. Many tubules are compressed or atrophied. Many other tubules are dilated. Among these dilated and compressed tubules is a considerable round cell infiltration. The atrophy of many tubules and the dilatation of others make it appear as if the glomeruli were closer together than normal. Some of the convoluted tubules present moderate acute change, the lumen being filled with necrotic debris.

Summary: Chronic change with a minimum of acute degeneration.

DISCUSSION

The kidneys of rabbits that died following a single injection of uranium presented extreme changes in the cells lining the convoluted tubules. In some instances this consisted of swelling of the cells until the lumen of the tubule was obliterated. The cells themselves contained many fine granules and the nuclei were indistinct. In other instances cells were loosened from the tubules and the nuclei were indistinct or or could not be found. Still further injury was found consisting of necrosis of a large proportion of the cells lining many of the convoluted tubules. In such instances the functions of the kidney were practically suspended with the result that there was a marked increase in the nonprotein nitrogen and the urea nitrogen of the blood. At the same time, there was a marked disturbance of the acid-base balance, the alkali reserve and the carbon dioxid of the blood becoming gradually lower until death. If, however, the animal does not succumb and repair or replacement of the damaged cells lining the convoluted tubules takes place, an altered cell results. This cell is not so large as its predecessor. Its nucleus is larger in proportion to the size of the cell than formerly and often pushes the outer edge of the cell toward the lumen of the tubule. These changes have been described by MacNider [17] and others. Frequently, young animals are able to so completely repair this damage that the acid-base equilibrium returns to normal and the only evidence of kidney damage that may remain is a slightly lowered phthalein output or traces of albumen in the urine.

17. MacNider, William de B.: A Pathologic Study of the Naturally Acquired Chronic Nephropathy of the Dog, J. M. Research **34**:177, 1916.

But, following repeated injections of uranium, there occur, in addition to the changes in the cells lining the convoluted tubules and the limbs of Henle, changes in the glomeruli, Bowman's capsule and the walls of the capillaries. Further, a diffuse round cell infiltration takes place throughout the cortex and following this there is an actual deposition of scar tissue in these areas. If the experiment is carried on for a sufficient length of time, a pronounced chronic nephritis which resembles chronic diffuse nephritis in man, results. During the development of this nephritis and after its establishment a disturbed acid-base balance persists. During the acute exacerbations there has been a heaping up of nonprotein nitrogen and urea nitrogen in the blood. At the same time there has been a diminution in the total nitrogen, urea nitrogen and to a less extent of the creatinin and uric acid nitrogen in the urine. This is followed in from four to five days by an increased excretion of these substances and a gradual fall of the heaped up products in the blood. When the chronic nephritis is established a moderate increase in the nonprotein nitrogen and urea nitrogen persists but, at the same time, there is an increase in the excretion of the various urinary constituents.

MacNider [18] observed that the first change in experimental nephritis induced by uranium has been a disturbance of the acid-base balance. He has also shown that there is a close relation between the acid-base balance and the ability of the kidney to continue its functions as determined by the various functional tests and the blood and urine chemistry. Our work has corroborated this. As stated before, we have found that lowered carbon dioxid and alkali reserve readings precede any other change. Whether this disturbed balance effects the early histologic changes that occur in the liver and kidney cells has not been proved, but it seems very probable.

Whether a disturbed acid-base balance has an etiologic relationship to beginning interstitial nephritis in man is a pertinent question. The urines of patients with chronic interstitial nephritis are strongly acid. They frequently have hydrogen ion concentrations of from 5.5 to 6. Sansum [19] has been able to correct this by a basic diet. When this is effected such patients whose blood pressures are increased often have a decided fall in both the systolic and diastolic readings. These lowered readings have been maintained for months at a time in patients whom we have followed. Whether further degenerative changes in an interstitial nephritis can be deferred by keeping the reaction of the urine at or

18. MacNider, William de B.: The Changes Induced in the Kidney When an Acute Injury Is Superimposed in a Chronic Glomerulonephropathy. A Functional and Pathologic Study, Southern M. J. **14**:357, 1921.

19. Sansum, W. D.: The Use of Basic Diets in the Treatment of Nephritis, California State J M. **20**:1, 1922.

about the neutral point, that is, a hydrogen ion concentration of 7, is an interesting question. In endeavoring to answer it one must be mindful of the long periods of latency that frequently occur without any kind of treatment.

The relation between the nonprotein nitrogen and the urea nitrogen of the blood is a definite one in human interstitial nephritis. We have found this to be so in experimental uranium nephritis. Normally the urea nitrogen is 50 per cent. of the nonprotein nitrogen, but as the nonprotein nitrogen increases in amount, the urea nitrogen increases at a faster rate, so that when the nonprotein nitrogen reaches 100 mg. per hundred cubic centimeters of blood, the urea nitrogen is then usually about 85 per cent. of the nonprotein nitrogen.

The phenolsulphonephthalein readings at the beginning of our experiments varied from 80 to 91 per cent. output in two hours. The rabbit at the time of the injection of the phenolsulphonephthalein had 75 c.c. of water by stomach tube. During the latter stages of our experiments, the phenolsulphonephthalein readings varied from 10 to 18 per cent. For a few days following some of the larger injections the output was lower than this.

Christian [20] has recorded a fall in the phenolsulphonephthalein in acute nephritis in patients when they start to improve clinically. We did not make phenolsulphonephthalein determinations frequently enough to determine this, but in some of our animals we observed a secondary acidosis after an animal started to recover. It is interesting to note that MacNider,[21] working with dogs, also discovered a secondary fall in phenolsulphonephthalein after the animal began to recuperate from the uranium intoxication.

CONCLUSIONS

Varying stages of nephritis in rabbits have been produced by the injection of uranium nitrate. Large single doses have produced an extreme degeneration of the cells lining the convoluted tubules and the loops of Henle. Repeated doses over a long period of time have produced a chronic nephritis, comparable to chronic diffuse nephritis in man.

After repeated injection, very large doses of uranium may be given. This dosage reached 50 mg. of uranium nitrate in a 6 pound rabbit.

Initial injections of uranium resulted in a sharp rise in the nonprotein nitrogen and the urea nitrogen in the blood. After a chronic nephritis

20. Christian, H. A.: Some Phases of the Nephritis Problem, Am. J. M. Sc. **151**:625, 1916.

21. MacNider, William de B.: A Functional and Pathologic Study of the Chronic Nephritis Induced in a Dog by Uranium Nitrate, J. Exper. M. **29**: 513, 1919.

had been established, these constituents were continuously higher than normal, but were often little altered following the injection of from 40 to 50 mg. of uranium.

When charted on logarithmically ruled paper, the total nitrogen, urea nitrogen, and the uric acid nitrogen in the urine are all roughly proportionate in their variations among themselves and to the amount of urine in cubic centimeters.

The organic acids in the urine are also roughly proportionate to the foregoing.

The increases and decreases of the ammonia in the urine follow the direction of the curves of the foregoing but in an exaggerated way, generally dropping lower and rising higher (proportionately) than the others.

The curve for the urea nitrogen in the urine is somewhat flatter than the others, dropping and rising less, but in the same general direction.

The nonprotein nitrogen, urea nitrogen and carbon dioxid in the blood do not parallel any of the above curves. The nonprotein nitrogen and the urea nitrogen follow each other closely. Either would seem as satisfactory as the other in determining the kidney's excretory ability.

The creatinin and uric acid nitrogen of the urine showed less deviation from the normal than any of the constituents studied.

Acetone and diacetic acid were irregularly present in the urine following the uranium injections.

The first change following an injection of uranium was found to be a disturbance of the acid-base balance. At about the same time certain histologic changes were found in the liver and kidney.

The organic acids of the urine, while a fair index of the degree of acidosis, were not found as dependable as the alkali reserve and carbon dioxid of the blood serum.

The relative degree of acidosis as determined by the carbon dioxid and alkali reserve readings and by the increased output of organic acids and ammonia in the urine coincided pathologically with the extent of cell destruction in the kidney.

THE VITAL CAPACITY IN HYPERTHYROIDISM WITH A STUDY OF THE INFLUENCE OF POSTURE

A PRELIMINARY REPORT *

I. M. RABINOWITCH, M.D.

MONTREAL

The data presented here form part of the observations made on the vital capacity in cases of hyperthyroidism. Although a number of such observations have been made in a wide range of similar cases of varying severity, it would be unwise at the present time to formulate definite conclusions of too sweeping a character. Sufficient has, however, been done to demonstrate the clinical utility of the test, and to stimulate further studies.

Although this laboratory procedure is old [1] it has not received, relatively, the same consideration as have many other laboratory methods. This, in great part, was due to the lack of knowledge of certain factors which must govern the interpretation of findings, presenting such wide, and at times irregular variations, even in the normal subject. The very thorough work of Dreyer, Peabody and Wentworth, Lundsgaard and Van Slyke, and West [2] in establishing "normals" as units for comparison demonstrates that this simple laboratory procedure is a satisfactory means of estimating the general physical status of a person. Whether the diminution of the vital capacity is due to physical factors, such as diminution of the lung volume, loss of elasticity of lung tissue, etc., or to chemical changes which influence the respiratory center, etc., is still problematic. This, however, does not vitiate the clinical value of the test.

Observations, some of the data of which are shown, were made in three groups of cases: (*a*) hyperthyroidism of the exophthalmic goiter type; (*b*) hyperthyroidism secondary to previously existing adenoma, and (*c*) hyperthyroidism following the administration of thyroid extract. The purpose in this report is to show, graphically, the general relation that has been found between the degree of hyperthyroidism as estimated by the basal metabolic rate and the vital capacity. The detailed results of these studies, in which an

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* From the Department of Metabolism, Montreal General Hospital.

1. Hutchison, J.: On the Capacity of the Lungs and on the Respiration Functions, with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, Med. Chir. Tr. Lond. **29**:139, 1846.

2. West H. F.: Clinical Studies on Respiration, Arch. Int. Med. **25**:306 (March) 1920. Dreyer, G.: The Assessment of Physical Fitness, London, Cassell & Co.; Lundsgaard C., and Van Slyke, D. D.: The Relation Between Thorax Size and Lung Volume, J. Exper. Med. **27**:65, 1918. Peabody, F. W., and Wentworth, J. A.: Clinical Studies on Respiration, Arch. Int. Med. **20**: 443 (Oct.) 1917.

attempt is made to determine the factors which operate in determining the vital capacity and in which the clinical pictures are analyzed and correlated with the laboratory findings form part of a report to be published separately, with the accumulation of more data.

The determination of the value of any physical property is always subject to error, so that the results of observations made even under the most ideal conditions can be but approximations of the true values. The chief sources of error are: (*a*) errors of observations; (*b*) errors of the apparatus used, and (*c*) neglect of certain other factors which exercise an appreciable effect on the results. Although the first two may be controlled with a reasonable degree of accuracy in the estimation of the vital capacity, the last is of special importance for consideration, since at times the clinical condition demands that the patient be disturbed as little as possible. Thus, it was not always practical to place the patient in the most suitable posture for the test. Results obtained in an abnormal posture must necessarily lead to results varying from the "normal" even in the healthy subject.

Therefore, a series of values for the vital capacity were obtained in the normal posture, and in a standard recumbent posture, with the subject in the dorsal decubitus position, and the head and shoulders elevated at an angle of about 30 degrees. This was done with the intention of deriving a constant whereby it might be possible to calculate the normal vital capacity, where it is clinically possible to determine the latter, only in the recumbent position. For this purpose a table of values was drawn showing the vital capacity in the normal position, in the recumbent position, and the percentage which the normal is of the recumbent, that is, $\frac{\text{normal vital capacity}}{\text{recumbent vital capacity}} \times 100$. The normal male subjects were members of the hospital staff and medical students. The normal female subjects were undergraduate nurses assumed to be healthy, having had a thorough physical examination before admission to the training school for nurses. The vital capacity was measured with a spirometer which gave readings within an error of 5 c.c. The procedure necessary to obtain results was first demonstrated to the subject, and the maximum reading of five determinations was accepted as the final result. Since it was necessary to determine the body surface in the calculation of the basal metabolic rate, it seemed practicable to apply this unit in the calculation of the vital capacity.

The method of obtaining the body surface was that of DuBois and DuBois.[3] Calculated on the basis of liters of air expired per square meter of body surface, it will be noted in column 7 that the average result obtained was 1.93 for females. This approximates very closely that obtained by West [2] which was 2.07. The standard adopted, there-

3. DuBois, D., and DuBois, E. F.: The Measurement of the Surface Area of Man, Arch. Int. Med. **15**:868 (June) 1915.

fore, that of West,[2] was 2.0 for females and 2.5 for males. On this basis, 88.9 per cent. of the normal subjects in the normal posture showed a vital capacity within the limits of normal variation allowed; ± 10 per cent. The combined results obtained by employing the above units

TABLE 1.—*Data of Fifty Cases. Influence of Posture on Vital Capacity*

Number	Name	Vital Capacity in Normal Posture (a)	Vital Capacity in Recumbent Posture (b)	$\frac{a}{b} \times 100$	Body Surface, Sq. M. (c)	$\frac{a}{c}$	Calculated Vital Capacity
1	HV	3,230	3,010	107.3	1.60	2.01	3,235
2	PS	3,220	3,000	107.0	1.75	1.84	3,225
3	AR	2,960	2,890	102.4	1.51	1.95	3,106
4	ABP	3,310	3,210	103.1	1.56	2.12	3,450
5	KW	3,350	3,230	103.7	1.78	1.88	3,472
6	AC	3,450	3,270	105.5	1.69	2.04	3,515
7	CD	3,100	2,820	109.9	1.49	2.08	3,061
8	SM	3,430	3,180	107.8	1.59	2.11	3,418
9	HI	3,170	2,910	108.9	1.65	1.92	3,128
10	MI	3,530	3,350	105.3	1.65	2.14	3,601
11	AE	2,860	2,840	100.3	1.52	1.88	3,053
12	GA	2,440	2,440	100.0	1.85	1.31	2,623
13	GC	3,075	2,925	105.1	1.45	2.12	3,144
14	NEP	3,190	2,990	106.6	1.66	1.92	3,214
15	LJG	3,090	2,990	103.3	1.82	1.69	3,214
16	CC	3,300	2,900	113.7	1.62	2.03	3,117
17	TLC	3,200	2,930	109.2	1.86	1.72	3,149
18	DDA	2,700	2,600	103.7	1.50	1.86	2,891
19	AMF	3,415	3,415	100.0	1.76	1.93	3,671
20	ABW	2,875	2,525	113.8	1.56	1.83	2,714
21	LJS	3,040	3,040	100.0	1.46	2.08	3,268
22	OE	3,400	3,100	109.6	1.77	1.92	3,332
23	OM	3,760	3,685	102.0	1.92	1.95	3,961
24	MHH	3,660	3,460	105.8	1.68	2.17	3,719
25	MON	3,065	2,565	119.4	1.58	1.93	2,757
26	IMC	5,820	5,620	105.5	1.80	2.05	5,811
27	ANH	2,350	1,850	127.0	1.55	1.51	1,988
28	GS	3,180	2,880	110.4	1.69	1.88	3,096
29	GMD	3,420	2,920	117.1	1.78	1.92	3,139
30	EMH	3,365	2,990	112.5	1.70	1.98	3,214
31	FCS	3,765	3,740	100.6	1.44	1.91	4,020
32	WAS	3,190	2,240	116.4	1.58	2.01	2,455
33	B	4,875	4,775	102.0	1.30	2.11	5,133
34	ZAS	3,010	2,760	109.0	1.55	1.94	2,967
35	MEE	3,400	3,000	113.3	1.72	1.98	3,225
36	IGJ	3,195	3,195	107.5	1.63	1.95	3,434
37	IS	2,485	2,385	104.1	1.48	1.69	2,563
38	CD	3,230	2,970	108.2	1.52	2.11	3,092
39	McG	4,245	3,995	106.2	1.74	2.43	4,294
40	LD	3,290	2,890	113.8	1.75	1.88	3,106
41	EJ	2,870	2,270	126.4	1.56	1.84	2,440
42	EVB	2,645	2,545	100.0	1.52	1.74	2,843
43	MOJ	3,155	3,105	101.5	1.61	1.95	3,337
44	NCM	3,050	2,960	103.3	1.48	2.06	3,171
45	SAB	3,090	3,090	100.0	1.68	1.83	3,321
46	AEF	2,625	2,110	126.8	1.53	1.75	2,268
47	SR	3,530	3,460	102.0	1.84	1.92	3,742
48	GP	3,680	3,660	100.6	1.72	2.14	3,934
49	LS	3,270	3,060	106.9	1.65	1.98	3,289
50	APM	2,750	2,720	101.2	1.48	1.85	2,924

were: (*a*) Within normal limits, 88.9 per cent.; (*b*) between 80 and 90 per cent. of normal 4.4 per cent.; (*c*) between 80 and 85 per cent. of normal 2.2 per cent.; (*d*) between 75 and 80 per cent. of normal 2.2 per cent.; (*e*) between 120 and 125 per cent. of normal 2.2 per cent.

Column 4 shows the results of fifty analyses made in the recumbent position. With the exception of five subjects in this group in whom no difference was noted, the effect of the recumbent position was to diminish the air expired from 20 to 600 c.c. Although in many cases

the difference is not of sufficient magnitude to affect the results from a clinical point of view, it seemed that a greater value could be attached to them, if it were possible to adopt a constant correction, whereby the actual and calculated values would vary within narrower limits.

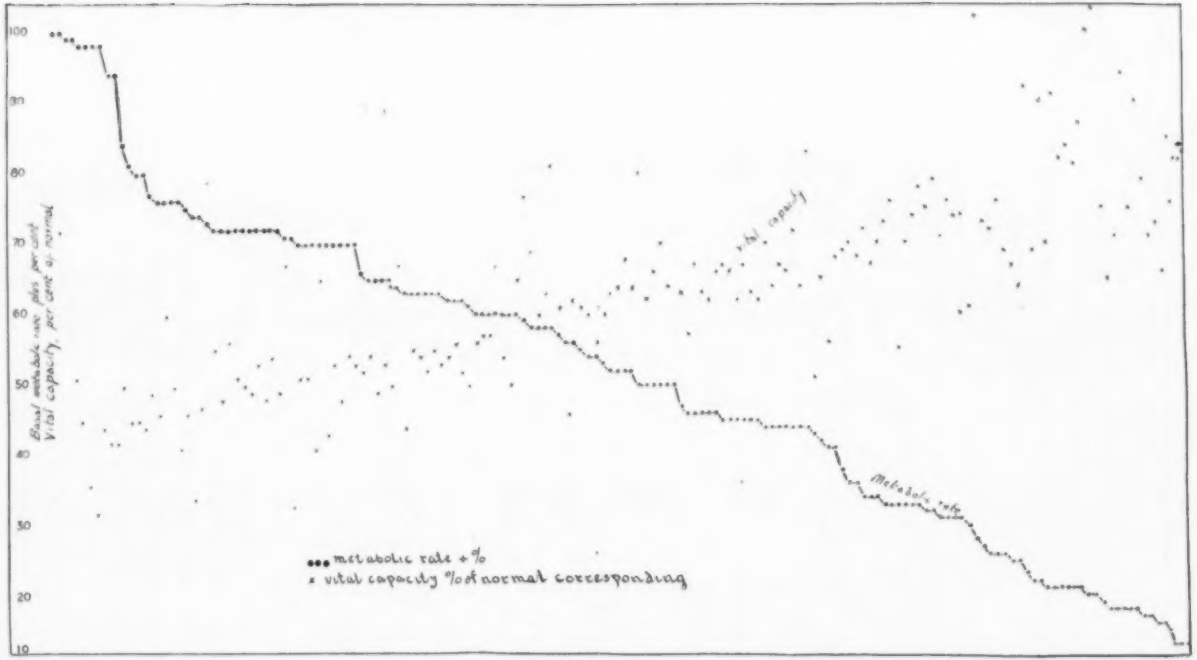
The arithmetical mean of all values for the factor $\frac{\text{normal vital capacity}}{\text{recumbent vital capacity}} \times 100$ was 107.5; that is the vital capacity obtained in the normal posture was 7.5 per cent. greater than that obtained in the recumbent posture. Mathematicians have for years known, and Krogh [4] has recently pointed out that the average of a series of measurements (i. e. the arithmetical mean) is not the most probable true value. The most probable true value is arrived at by the application of the statistical theory of errors. In this calculation the minimum regarded as sufficient is the determination of the mean error or standard deviation of a single determination, and the mean error of the average. In these studies this has been considered. When one appreciates the numerous possible factors which might influence the results in the estimation of the vital capacity, however true this may be with regard to the purely arithmetical value of the result, such refined calculation, involving the statistical theory of errors, would probably give an impression that was not intended; that is, the extreme accuracy with which this physical measurement can be made. Since every physical measurement of any description involves some error or can be carried out with only a certain degree of accuracy, it is evident that the number expressing the value of a property depending on a measurement can only be approximate. However finely we may calculate the vital capacity, our results cannot increase the accuracy of the value beyond the limits of experimental error. Therefore, from the observations made, the correction constant accepted was 1.075; that is, the product obtained by multiplying the observed volume of gas expired in the recumbent position by 1.075 was accepted as the volume that would be obtained if the subject were in the normal posture.

It will be noted from the values in column 8 that by applying this correction and thus increasing the observed vital capacity obtained in the recumbent position, the actual (column 3) and calculated (column 8) corresponds remarkably well.

On this basis, 86.4 per cent. of the same normal subjects whose vital capacity was taken in the recumbent posture showed variations within the normal limits only, allowing $\pm$ 10 per cent. variation. This compares favorably with that obtained in the normal posture—88.9 per cent.

In the graphic chart is shown the general relation between the decrease in the vital capacity and the severity of the hyperthyroidism as estimated by the basal metabolic rate. The latter varied from + 100

4. Krogh, A.: The Respiratory Exchange of Animals and Man. Monographs on Biochemistry, London, Longmans, Green & Co.



Relation between decrease in vital capacity and degree of hyperthyroidism as estimated by basal metabolic rate.

per cent to + 16 per cent. and the vital capacity varied from 30 to 101 per cent. of normal. It will be noted that in only three cases was the vital capacity above the normal, and five values were within the normal limits of variation, ± 10 per cent.

A noteworthy observation was that all patients having a vital capacity of 40 per cent. or under of normal were bedridden, which agrees with the observations of Peabody on cases of heart failure. Table 2 shows the average vital capacity found in relation to the metabolic rate:

An additional interest is attached to these observations, since we have here a possible explanation of the dyspnea observed in cases of severe hyperthyroidism, excluding that due to chemical stimulation of the respiratory center or cardiac embarrassment. Peabody [5] first demonstrated that an important factor in producing dyspnea may be the inability to breathe deeply. He studied mathematically the problem of the maximum minute volume of pulmonary ventilation and found that

TABLE 2.—*Average Vital Capacity in Relation to Metabolic Rate*

Metabolic Rate, Percentage Above Normal	Vital Capacity, Percentage of Normal
Between 100-90	42
90-80	46
80-70	50
70-60	57
60-50	63
50-40	65
40-30	71
30-20	79
20	79

the latter was partly a function of the vital capacity. This appears to have an application to hyperthyroidism. Associated with an increase in the basal metabolic rate, the oxygen consumption and the carbon dioxid production increases. To acquire the former and excrete the latter an increase in the pulmonary ventilation, including the respiration rate and ventilation rate, is required. A lower vital capacity may thus be an important factor in the production of dyspnea in severe cases of hyperthyroidism. This problem is being investigated.

5. Peabody, F. W.: A Mechanical Factor in the Production of Dyspnea in Patients with Cardiac Disease, Arch. Int. Med. **20**:443 (Sept. 1917; Sturgis, C. C.; Peabody, F. W.; Hall, F. C., and Fremont-Smith, F. Jr.: The Relation of Dyspnea to the Maximum Minute Volume of Pulmonary Ventilation, Arch. Int. Med. **29**:236-244 (Feb.) 1922; Peabody, F. W.; Wentworth, J. A., and Barker, B. I.: The Basal Metabolism and the Minute Volume of the Respiration of Patients with Cardiac Disease, Arch. Int. Med. **15**:468-478 (Sept.) 1917.

STUDIES ON THE POTASSIUM CONTENT OF HUMAN SERUM *

LAWSON WILKINS, M.D. AND BENJAMIN KRAMER, M.D.
BALTIMORE

OBSERVATIONS OF OTHER WORKERS

The normal potassium content of the human blood serum has been determined by different workers with various results, as shown in Table 1. The older writers, Schmidt and Wanach, worked with inferior chemical methods. The more recent workers have all obtained fairly uniform results with the exception of Richter-Quittner whose figures are considerably higher than those reported by others. Richter-Quittner found the concentration of potassium in ashed serum to be considerably higher than that found in the ultrafiltrate from the same serum. He argued from this that a portion of the potassium was bound to serum protein. Kramer and Tisdall, however, have found

TABLE 1.—*Potassium Content of Human Serum Found by Various Observers*

	Mg. per 100 C.c.	
Schmidt, C.,[1] 1850	31-33	
Wanach, R.,[2] 1888	15-21	
Richter-Quittner,[3] 1921	50-80	in ashed serum
	20-60	by the ultrafiltrate method
Macallum, A. B.,[4] 1917	19-21	in blood plasma
Meyers, V. C., and Short, J. J.,[5] 1921	14-18	
Kramer, B., and Tisdall, F.,[6] 1921	18-21	

no discrepancy between the results obtained on ashed serum and those by direct precipitation from the same serum.[7] They have emphasized the remarkable constancy of the concentration of potassium in normal human serum.

A number of investigators have studied the potassium of the serum in pathologic conditions. Schmidt obtained values of from 43 to 72 mg. per hundred cubic centimeters of the serum of patients suffering from cholera and 63 mg. in a patient with "anasarca without albumin-

* From the Department of Pediatrics, Johns Hopkins University.

1. Schmidt, C.: Characteristik der Epidemischen Cholera, Leipzig und Mitau, 1850, pp. 29 and 30.
2. Wanach, R.: Jahresb. d. Thier Chemie **18**:88, 1888.
3. Richter-Quittner: Biochem. Ztschr. **24**:110, 1921.
4. Macallum, A. B.: Tr. College of Physicians, Philadelphia **39**:286, 1917.
5. Meyers, V. C., and Short, J. J.: J. Biol. Chem. **48**:83, 1921.
6. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **46**:339, 1921.
7. This finding does not contradict the possible existence of compounds of protein with potassium in serum.

uria." Clausen [8] found from 53 to 90 mg. potassium in the plasma of patients with various diseases. Kramer and Tisdall reported in twelve children suffering from various febrile diseases values for the potassium of serum ranging from 35 to 70 mg. per hundred cubic centimeters. They were aware, however, that the potassium concentration increases when the serum is allowed to remain in contact with the clot and, therefore, suggested that the observed increase of the potassium of the serum of pathologic cases required further investigation. Meyers and Short, on the other hand, could find no increase in the potassium in any of the diseases which they studied. In ten patients suffering from a variety of pathologic conditions such as polycystic kidneys, cardiac decompensation and anasarca, essential hypertension, eclampsia, carcinoma, pneumonia, diabetic coma and syphilis, their values ranged from 15 to 20 mg. in all except three instances. These three serums, which gave values of 24, 28 and 35 mg., respectively, had been allowed to stand a considerable length of time before separation from the

TABLE 2.—*Potassium Content of Serum at Varying Periods*

Time Before Separating Serum	Potassium, Mg. per 100 C.c.
0	22.5
1 hour	23.6
2 hours	23.6
4½ hours	26.1
9 hours	26.5
24 hours	36.1
48 hours	41.9
72 hours	59.1 slight hemolysis present
96 hours	61.9 slight hemolysis present

clot. The same authors found in seven cases of advanced nephritis, showing marked nitrogen retention, from 10 to 20 mg. of potassium per hundred cubic centimeters of serum.

SOURCES OF ERROR IN THE ESTIMATION OF POTASSIUM

In this study we have used the method described by Kramer and Tisdall. Because of the higher results obtained by Kramer and Tisdall with the serum of febrile patients, it was decided to investigate further the factors which might lead to errors in the estimation of potassium in the serum. Since the red blood cells contain an enormous store of potassium (from 410 to 440 mg. per hundred cubic centimeters) it is evident that any hemolysis will liberate potassium into the serum. It was found that, when even the slightest trace of hemolysis could be noted, the potassium content of the serum was greatly increased—frequently to 30 and 60 mg. per hundred cubic centimeters. Likewise, when the serum stands in contact with the clot for a considerable length of time, potassium diffuses out from the corpuscles. The rate of this diffusion is shown in the following experiment: Blood was drawn

8. Clausen, S. W.: J. Biol. Chem. **36**:479, 1918.

from a subject into a number of tubes, which were allowed to stand at room temperature for varying lengths of time before centrifuging and separating the serum from the clot. At varying intervals the serum was separated and samples analyzed for potassium. The results are given in Table 2. The concentration of potassium in the serum remains approximately unchanged for two hours, then mounts quite rapidly so that within twenty-four hours there is a marked increase, even though there is no hemolysis.

In one case of epidemic encephalitis, blood was taken by cardiac puncture fifteen minutes after death and the serum was separated immediately. The potassium was found to be increased to 45 mg. Meyers and Short have noted a similar increase after death in both blood serum and spinal fluid. Evidently some change occurs at death which allows a rapid diffusion of potassium from the cells.

After serum has once been separated from the corpuscles it can be kept for a considerable length of time without affecting the esti-

TABLE 3.—*Potassium Values in Various Pathologic Conditions*

Serum No.	Diagnosis	Potassium, Mg. per 100 C.c.
1	Puerperal sepsis	19.2
2	Pyelitis	18.0
3	Pneumonia	17.7
4	Tonsillitis and cervical adenitis	23.0
5	Pneumonia	20.9
6	Scarlet fever	20.3
7	Subacute endocarditis	20.9
8	Pneumonia	18.1
9	Diabetes mellitus	20.2
10	Diabetes mellitus	19.9
11	Pernicious anemia	22.0
12	Pernicious anemia	21.7

mation of potassium. Even after standing for a month such serum gave reliable values for potassium by the method used in this investigation.

We have found, then, that the method of Kramer and Tisdall is reliable within an error of ± 5 per cent., as stated by the authors. To obtain, however, the true concentration of potassium as it exists in vivo precautions must be taken (1) to remove all the red blood cells by centrifuging the serum, (2) to prevent hemolysis, (3) to separate the serum from the clot within half an hour after the blood is drawn. Observing these precautions we have invariably found the potassium content of normal serums to be from 18 to 22 mg. per hundred cubic centimeters.

POTASSIUM OF THE SERUM IN VARIOUS PATHOLOGIC CONDITIONS

Table 3 shows the values for potassium which we found in twelve persons suffering from various pathologic conditions. In all of these a normal content of potassium was found. In the two cases of per-

nicious anemia studied, there was evidence of marked hemolysis occurring within the body, as shown by the increase of bile pigments in the serum and of the urobilin in the urine. In spite of the fact that this destruction of red blood cells must liberate potassium, the concentration of this element in the serum was apparently maintained at the normal level.

POTASSIUM OF THE SERUM IN NEPHRITIS

The possibility of potassium retention in nephritis has aroused considerable interest. Smillie [9] reported that one nephritic patient to whom

TABLE 4.—*Potassium of the Serum in Nephritis*

Serum No.	Patient and Age	Diagnosis	Date	Edema	Phthalein, per Cent.	Serum Nonprotein Nitrogen, Mg. per 100 C.c.	Serum Protein, per Cent.	Serum Potassium, Mg. per 100 C.c.	Condition on Discharge
13	C. S. 5 yrs.	Nephrosis	1/20/22 3/10/22	Very marked generalized	.. 70	.. ..	6.4 6.2	20.9 20.3	Unimproved
14	E. McC. 2 yrs.	Nephrosis	3/10/22	Very marked generalized	..	..	6.6	21.5	Unimproved
15	M. G. 9 yrs.	Acute glomerulonephritis	1/20/22	None	..	..	8.0	22.0	Well
16	W. S. 7 yrs.	Acute glomerulonephritis	6/28/21	Slight, face and ankles	45	25	....	23.5	Well
17	A. F. 20 yrs.	Acute nephritis, bichlorid poisoning	11/ 8/21	Slight, face	..	100	....	25.1	Died
18	R. P. 21 yrs.	Subacute nephritis	1/25/22 2/ 6/22	None	75 48	31 43	9.0 9.0	22.4 25.8	Worse
19	M. P. 16 yrs.	Chronic nephritis (acute exacerbation)	11/25/22 2/ 6/22	Slight, face	39 50	34 ..	8.2 7.4	19.2 18.7	Improved
20	G. T. 45 yrs.	Chronic nephritis, hypertension	2/ 6/22	Slight, ankles	30	43	6.5	26.3	Unimproved
21	J. D. 47 yrs.	Chronic nephritis, hypertension, myocardial insufficiency	1/25/22	None	47	27	8.4	21.3	Improved
22	P. McE. 36 yrs.	Chronic nephritis, hypertension, arteriosclerosis, myocardial insufficiency	2/ 6/22	Marked, legs	16	125	7.5	26.0	Died

10 gm. potassium chlorid was administered showed marked toxic symptoms which he attributed to the potassium. Rabbits with uranium nephritis died with great suddenness following the ingestion of 1 gm. potassium chlorid, while normal rabbits took from 3 to 4 gm. without ill effect. He believed that this was due to the failure of the damaged kidneys to excrete potassium properly. Smillie did not determine the potassium content of the blood. His experiments, however, suggested that there might be an increase of the potassium in the blood of nephritics sufficient to account for some of the toxic symptoms. Meyers and Short found no increase in either the serum or whole blood of

9. Smillie, W. G.: Arch. Int. Med. **16**:330 (Sept.) 1915.

seven patients with advanced nephritis showing marked nitrogen retention. Loeb, Atchley and Palmer,[10] likewise, have found no increase in the serum potassium in nephritis with extensive ascites.

In Table 4 we have recorded our findings in a number of different types of nephritis and nephrosis. In most instances the potassium was found to be within the normal limits (from 18 to 22 mg.), but in four serums (Nos. 17, 18, 20 and 22) there was a slight increase to 25 and 26 mg. The two children with nephrosis (Nos. 13 and 14) both had a very marked generalized edema and ascites but showed no increase of potassium in the serum. Several of the patients with nephritis had slight edema, but we have had no opportunity to study any cases of so-called chronic parenchymatous nephritis with extensive anasarca. Accordingly we cannot state whether this type of the disease might be associated with a more marked increase of potassium in the serum than we have found in any of our cases. The four serums in which we did find a slightly increased amount of potassium were from patients with a definite nitrogenous retention and a diminished phenolsulphonephthalein excretion. Two of these patients (Nos. 17 and 22) died of uremia. One patient (No. 18) on January 25 had a phenolsulphonephthalein excretion of 75 per cent. in two hours and a nonprotein nitrogen of 31 mg. per hundred cubic centimeters of blood. At this time the serum potassium was 22.4 mg. The patient became clinically worse and on February 6 the phenolsulphonephthalein excretion had decreased to 45 per cent. and the blood nitrogen had increased to 43 mg. Coincident with these changes, the potassium of the serum had risen to 25.8 mg.

Although these studies have shown that there may be this slight increase of the potassium of the serum in nephritis, we feel that the increase is so small that we are not justified, at the present time, in attributing toxic symptoms to it. We have, on the contrary, been able to show that by the ingestion of potassium chlorid the potassium of the serum may be raised for a short period of time as high as 35 mg. per hundred cubic centimeters without producing any marked toxic symptoms. Of course, the retention of potassium in the tissues is not ruled out by our findings on the serum and still must be considered as a possible toxic factor in nephritis.

POTASSIUM OF THE SERUM IN TETANY

The only other disease in which we have found the potassium content of the serum increased is tetany. In four out of five cases studied, the potassium was moderately increased (from 23 to 29 mg.). These findings are the same as those of Kramer, Tisdall and Howland.[11] As

10. Loeb, Atchley and Palmer: J. Gen. Physiol. **4**:591, 1922.
11. Kramer, Tisdall and Howland: Am. J. Dis. Child. **22**:431 (Nov.) 1921.

shown by a comparison of the figures for potassium and calcium given in Table 5 no definite relationship between the increase of potassium and the decrease of calcium could be made out.

EFFECTS OF THE INGESTION OF POTASSIUM SALTS

We have attempted to determine to what extent the potassium of the serum may be increased by the ingestion of potassium salts. Two patients who had been receiving 1.3 gm. potassium iodid three times a day for a long period of time were found to have 20.4 and 21.9 mg. potassium, respectively, in 100 c.c. of serum. E. D. Osborne [12] has studied the effects on the blood serum of the administration of potassium and sodium iodids. He gave 1 gm., 5 gm. and 20 gm. of potassium iodid by mouth and noted that "this did not produce a corresponding rise in the potassium content of the blood serum, but, on the contrary, a definite rise in the sodium content almost equal to that following (the administration of equivalent quantities of) sodium iodid. Following the 20 gm. dose only a slight rise in the potassium content was noted." On the other hand, he found a marked rise of the iodin of the blood serum proteins after the administration of potassium iodid and only traces after the ingestion of sodium iodid.

TABLE 5.—*Potassium and Calcium Values in Tetany*

Serum No.	Age	Potassium, Mg. per 100 C.c.	Calcium, Mg. per 100 C.c.
23	7 months	29.0	5.7
24	3 years	18.9	4.6
25	6 months	27.0	7.2
26	5 months	23.7	5.1
27	7 months	23.1	6.0

TABLE 6.—*Results of Ingestion of Potassium Chlorid*

Amount Taken	Potassium of the Serum, Mg. per 100 C.c.			
	Before	1 Hour After	2 Hours After	3½ Hours
2 gm.	20.6	20.4	25.4	....
10 gm.	20.6	24.6	29.8	22.9
15 gm.	20.8	....	35.3	....

We have made observations after the administration of the chlorid instead of the iodid of potassium. Unlike the iodid, the chlorid of potassium when taken by mouth causes a very marked increase of the potassium of the serum. The results of this experiment are shown in Table 6.

One of us (W) ingested 2 gm., 10 gm. and 15 gm. potassium chlorid in 300 c.c. of water on three different occasions. The potassium of the serum was found to be raised to 25.4, 29.8 and 35.3 mg. per

12. Osborne, E. D.: J. A. M. A. **79**:615 (Aug. 19) 1922.

hundred cubic centimeters after these respective amounts. The maximum increase occurred in about two hours; after which there was a rapid return to normal. The normal level was reached in about three and one half hours. No subjective symptoms were experienced beyond some nausea and sweating after the largest dose. Electrocardiograms were made during the experiment by other members of the staff. Certain changes in the curves believed to be characteristic were found and are being studied further.

SUMMARY

1. To obtain a correct estimation of the concentration of the potassium of serum as it exists in the body, precautions must be taken to prevent hemolysis and to separate the serum promptly from the corpuscles.

2. The potassium of normal human serum is fairly constant, varying only from 18 to 22 mg. per hundred cubic centimeters.

3. The potassium content was within these limits in all pathologic conditions studied except nephritis and tetany.

4. In some cases of nephritis the potassium was increased to 25 and 26 mg. per hundred cubic centimeters.

5. In tetany there is usually a slight increase of the potassium to from 23 to 29 mg. There is no definite relationship between this and the decrease in the calcium.

6. Patients receiving potassium iodid 1.3 gm., three times a day, showed no increase in the potassium content of their serum.

7. The ingestion of 2, 10 and 15 gm. potassium chlorid raised the potassium of the serum to 25, 30 and 35 mg. per hundred cubic centimeters, respectively. No subjective effects were felt but changes in the electrocardiogram were observed.

SOME UNUSUAL DISTURBANCES OF THE MECHANISM OF THE HEART BEAT*

FRANK N. WILSON, M.D., AND GEORGE R. HERRMANN, M.D.
ANN ARBOR, MICH.

I

AN ECTOPIC TACHYCARDIA OF FIFTEEN MONTHS' DURATION

Attacks of simple paroxysmal tachycardia usually last but a few hours or at most a few days. Lewis [1] states that attacks which last a fortnight are rare and that longer attacks are unknown. D. C. Wilson [2] has recently reported an instance in which an attack of ten days' duration was followed by the development of gangrene of the forearm. This is the longest attack described in the recent literature. We were surprised, therefore, to encounter a patient with a tachycardia of this type that had persisted for approximately fifteen months.

CASE 1.—*History.*—Mr. E. K., and American student, aged 22, first seen by us in July, 1920. He complained of palpitation associated with rapid heart action. There was a history of whooping cough and measles in childhood, but none of rheumatic fever, chorea, scarlet fever or diphtheria. The patient had a severe atttack of tonsillitis in 1918 and another in 1919. The tonsils were removed in December of the latter year. In February, 1919, he burned his hand; the wound became infected, and there was a local cellulitis for two or three weeks, followed by lymphangitis, which spread up the arm and involved the axillary glands. The infected glands were incised and drained; hot boric packs were applied, and the wound was irrigated with surgical solution of chlorinated soda (Dakin's solution). Gradual recovery followed. About April 10, 1919, two root abscesses were discovered, and the teeth concerned were removed under nitrous oxid anesthesia. After the first return of consciousness, "things turned black," and he relapsed for a short time into an unconscious state. During the following night, he was awakened by the rapid beating of his heart, amounting to distressing palpitation. He was kept in bed for three months, but rest had no effect on the heart rate.

When the patient first came to us, the tachycardia had been present continuously since its onset about fifteen months before. He was conscious of his heart beat at all times and was a little short of breath, but his symptoms were not sufficiently severe to interfere with his usual activities. He was attending the summer school at Washington University. He had found that if he took small doses of digitalis (15 drops of the tincture three times a day) and "behaved himself," the heart rhythm was regular; when he kept late hours, took excessive exercise or left off the digitalis for ten days or two weeks, the rhythm became irregular. He had also discovered that by holding the breath and straining (Valsalva experiment) he could suspend the tachycardia for a few seconds.

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*From the Department of Internal Medicine, Washington University Medical School, and the Department of Internal Medicine, University of Michigan Medical School.

1. Lewis, Thomas: Clinical Disorders of the Heart Beat, Ed. 2, London, 1914.

2. Wilson, D. C.: Heart **8**:303 (Aug.) 1921.

Examination.—The apex beat was visible and palpable in the fifth interspace just outside the nipple line; the impulse was diffuse and poorly sustained. The heart rate was 164 per minute. There was a slight systolic thrill and a soft blowing systolic murmur at the mitral area. There was conspicuous pulsation in the veins of the neck and also in the left infraclavicular region. The cardiac dulness extended 3 cm. to the right and 10.5 cm. to the left of the midline in the fifth interspace. A teleoroentgenogram was made; the right border of the cardiac silhouette was 4 cm. and the left border 8 cm. from the midline. The patient was then asked to stop the tachycardia by the method described, and a second plate was made. The heart shadow was about 1 cm. larger in all dimensions than on the first plate. This is the usual effect of the Valsalva experiment. The patient's exercise tolerance was excellent, and the remainder of the examination was negative.

Electrocardiograms showing the cardiac mechanism and the effect of holding the breath and straining at the time of the patient's first visit are shown in Figure 1. These records show that the disturbance of the heart beat responsible for the tachycardia was identical with that which gives rise to simple paroxysmal tachycardia. Holding the breath and straining brought about a sudden cessation of the rapid beating, but after from one to five seconds, it invariably returned as suddenly as it had stopped. Vagal pressure was without effect.

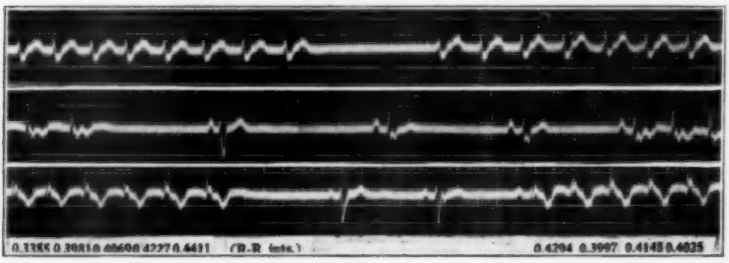

Fig. 1 (Case 1).—Periods of bradycardia produced by holding the breath and straining. The decrease in heart rate preceding the cessation of the tachycardia may be noted. One time division equals 0.2 second.

When first examined, the patient was taking small doses of digitalis according to his usual custom. He was asked to discontinue it for two weeks in order to determine the nature of the irregularity that, so he stated, appeared when the drug was not taken. He complied with our request, but the irregularity failed to appear. The patient was then given digitalis in large doses, in the hope that it might produce partial heart block and thus reduce the ventricular rate. After taking 23 c.c. of the tincture in a period of seven days, he returned with a complaint that, whenever he rested, and particularly at night, the heart rhythm became irregular. Periods of bradycardia similar to those which he was able to produce by holding the breath and straining occurred spontaneously with great frequency. They were accompanied by weakness and dizziness, and fear of death. The drug also produced anorexia and nausea. He refused to take more digitalis. When he first arrived at the laboratory, the heart rhythm was regular; but after he had rested for an hour or more, the periods of spontaneous bradycardia suddenly returned. The records obtained are shown in Figure 2. No further observations were made.

Comment.—So much for the essential features of the case; an unusual instance of very prolonged tachycardia of the simple paroxysmal type, with maintenance of surprisingly good cardiac function.

There are a few features of the electrocardiographic records which require brief comment. The ventricular complexes of the rapid rhythm are strikingly abnormal in form. They are diphasic, but of small amplitude; the Q-R-S interval is increased (0.1 second), and the Q-R-S group is curiously notched. That these complexes are of supraventricular origin is evident at once from Figure 2, in which complexes of the same form follow P deflections of normal outline. Their abnormal form must, therefore, be attributed to defective intraventricular conduction.

No auricular complexes can be identified during the rapid rhythm. In Leads II and III, the T deflection is curiously notched, and this notching may be due to the occurrence of an abnormal P deflection at this point. This view is supported by the absence of the notch from all complexes that follow normal P deflections except those that immediately precede the return of the tachycardia. This interpretation would, however, require the unwarranted assumption that the notch which deforms the final complex of each period of tachycardia represents a blocked auricular systole. A similar assumption would be necessary to explain the notching of certain idioventricular complexes that occur during the periods of bradycardia. Furthermore, we should be required to believe that the P-R interval of the first cycle of the returning tachycardia is much longer than the subsequent P-R intervals. In the face

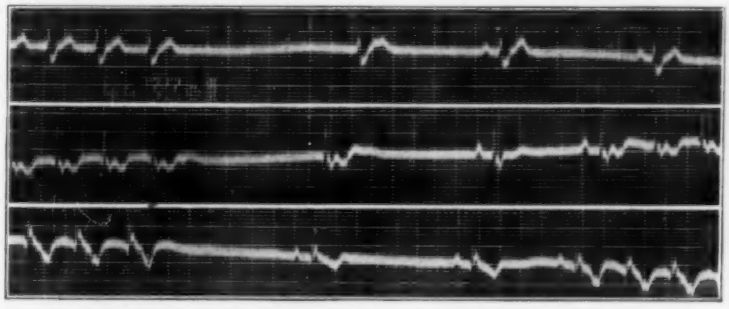

Fig. 2 (Case 1).—Periods of bradycardia which occurred spontaneously after digitalization.

of these difficulties, the auricular complexes cannot be located; and it is uncertain whether the tachycardia was of auricular or of atrioventricular origin.

In spite of the negative results of vagal pressure, the cessation of the tachycardia each time that the patient held the breath and strained must be attributed to vagus stimulation, and the spontaneous stops after digitalization undoubtedly had a similar origin. This effect of vagal stimulation is well known.

Many authorities advise against the administration of digitalis in cases of paroxysmal tachycardia. So far, we have not seen, in this disorder, high-grade heart block with consequent great reduction of the ventricular rate produced by it, but in several instances it has seemed that when digitalis was given the attacks were more easily controlled. We have also observed that drugs which produce a decrease in vagal tone, quinidin for instance, sometimes have the opposite effect.

The cessation of the tachycardia was invariably preceded by a conspicuous slowing of the ventricular rate. In this respect, the tachycardia differs from simple paroxysmal tachycardia, in which the end of the attack is not ordinarily preceded by slowing of the rate, whether the attack ends spontaneously or in response to vagal stimulation.

The cause of the bradycardia following the cessation of the rapid rhythm is not clear. It may have been the result of a continuation of the increased vagal tone, to which we have attributed the termination of the tachycardia; or it may be analogous to the bradycardia which follows the sudden production of A-V block. The idioventricular center, when suddenly called on to act as pacemaker, develops its rhythm slowly, and occasionally the sinus node, after it has been thrown out of action for a long period, seems to exhibit the same phenomenon (Lewis [3]).

The records show that, although the periods of bradycardia that were produced by respiratory experiments and those that occurred spontaneously after digitalization are similar, there is a distinct difference between them. The ventricular complexes which occur during the latter (Fig. 2) are all of the same form as the complexes of the paroxysmal series; but the complexes which occur during the former are very variable in form, and many of them are of obscure origin (Fig. 1). After digitalization, respiratory experiments produced a still greater variety of abnormal complexes. Occasionally, short stops were followed by resumption of the tachycardia without the occurrence of intervening nonparoxysmal beats (Fig. 1).

II

TOXIC DEPRESSION OF THE CONDUCTIVITY OF THE PURKINJE SYSTEM

CASE 2.—*History.*—Miss E. M. B., aged 22, admitted to Barnes Hospital, Feb. 26, 1920, complaining of persistent hiccup, vomiting and weakness, had left well until January 24, when she was seized with a severe headache and persistent anorexia. Two days later, she began to have pain in the upper abdomen. On the third day, she was nauseated; she vomited, and complained of pains in the ankles and feet. Her condition rapidly grew worse. One week before admission, her feet and legs began to swell. Three days later, she developed a persistent hiccup, and began to bleed from the nose and mouth, and to pass very small amounts of urine. She had had pain over the lower sternum and had been short of breath for some time, but lately these symptoms had become much worse.

Examination.—The patient lay slightly propped up in bed, hiccuping, and groaning with pain in the abdomen and chest. She was slightly apathetic, and the mucous membrane of the mouth and tongue was so dry as to interfere with speech. There was dried blood about the nose and mouth and fresh blood in the nasal and oral secretions. The skin and mucous membranes were very pale. The respiratory movements were very deep, and the respiration rate was 16 per minute. Many râles were heard over the lungs, especially at the bases, and the breath sounds were harsh. The area of cardiac dulness was slightly enlarged. The maximum impulse was felt in the third interspace, 5 cm. to the left of the midline. Less marked pulsation was felt in the fourth and fifth interspaces. On auscultation, a to-and-fro pericardial friction was heard over the central precordium and in the pulmonic area. The heart rate was 100 per minute; the rhythm was regular. The systolic blood pressure was 145, the diastolic, 95. There was ascites, with conspicuous edema of the ankles.

The blood examination revealed a high grade secondary anemia (1,900,000 red blood cells per cubic millimeter and 50 per cent. hemoglobin) and a polymorphonuclear leukocytosis (32,000 white cells per cubic millimeter). The urine contained a large amount of albumin, and the tests for acetone and diacetic acid were both positive. In the sediment, many red blood cells, white blood cells, and granular, cellular, and hyaline casts were found. The blood contained 407 mg. of nonprotein nitrogen per hundred cubic centimeters. The

3. Lewis, Thomas: The Mechanism and Graphic Registration of the Heart Beat, New York, Paul E. Hoeber, 1920.

diagnosis was chronic nephritis, with secondary anemia, uremia and *pericarditis brightique*. There was probably a profound acidosis also, though no tests to determine the degree of acidosis were made.

The electrocardiogram taken on the day of admission to the hospital is shown in Figure 3. It is of the type commonly considered indicative of preponderant hypertrophy of the left ventricle. The Q-R-S interval is slightly increased, measuring approximately 0.12 second. The P-R interval measures about 0.20 second; the R-T interval about 0.36 second. T2 and T3 are unusually tall and pointed.

The electrocardiogram taken on the following day about three quarters of an hour before death is shown in Figure 4. So far as the direction and the amplitude of the individual deflections are concerned, it is very much like the first curve. The electrocardiographic intervals, however, are very dif-

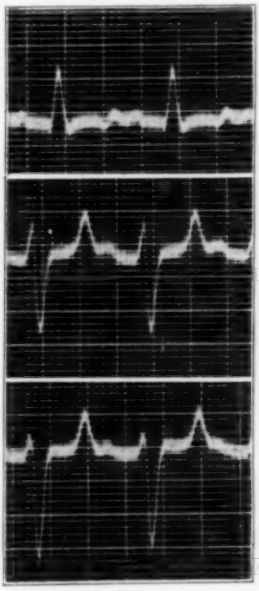

Figure 3

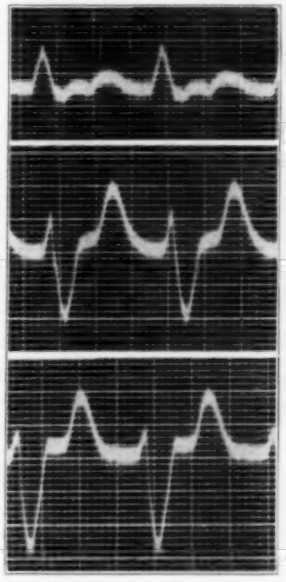

Figure 4

Fig. 3 (Case 2).—Electrocardiogram taken on the day of admission to the hospital.

Fig. 4 (Case 2).—Electrocardiogram taken on the following day, one-half hour before death.

ferent. The P-R interval cannot be determined because P is buried in the ventricular complex, but it is obviously greater than in Figure 3; the Q-R-S interval measures approximately 0.20 second and the R-T interval, about 0.56 second.

Comment.—How shall these curves be interpreted? It is possible that the first electrocardiogram represents incomplete right bundle branch block, and that when the second curves were made, the block had become complete. This interpretation does not explain the change in the P-R interval. Another explanation may be suggested. It seems possible that the profound toxemia

from which the patient died may have led to a progressive, general depression of the conductivity of the specialized cardiac tissues. At the time the second electrocardiogram was taken, several ventricular extrasystoles were recorded (Figure 5). It will be noted that they show the same broadening that is so striking in the complexes of supraventricular origin. In bundle branch block, extrasystolic complexes do not ordinarily differ from those recorded in cases which show no evidence of defective intraventricular conduction. It seems, therefore, that the peculiar form of these extrasystolic ventricular complexes supports the idea that there was a toxic depression of the conductivity of the Purkinje system.

In this connection, we may remark that the form of the extrasystolic complex is not without importance in interpreting electrocardiographic abnormalities. It is true that ventricular extrasystoles give rise to complexes of widely variable form, but in most instances it is possible for one who has read many electrocardiograms to say whether a given extrasystolic complex differs widely from the usual types that occur. It seems to us hazardous to attribute curves of small amplitude or curves with long Q-R-S intervals to widespread lesions of the ventricular muscle of the ventricular conducting system when extrasystolic complexes of what might be termed "normal outline" occur in the same record. Widespread lesions must affect the extrasystolic complex as well as the supraventricular complexes; and although small changes

Fig. 5 (Case 2).—Electrocardiogram taken immediately after that shown in Figure 5. The peculiar form of the extrasystolic complexes may be noted.

in the former cannot be recognized, great changes may be, especially when they are of the same class as those exhibited by the complexes of supraventricular origin. We have seen several cases in which this has been possible.

III

TRANSIENT COMPLETE BUNDLE BRANCH BLOCK

CASE 3.—*History.*—Mother L., a nun, was referred to the Washington University Heart Station for an electrocardiographic examination by Dr. Joseph Larimore, whose notes on the history and physical examination are given herewith.

In January, 1920, the patient complained of weakness and indefinite abdominal distress. The spleen and the liver were enlarged, and the white blood cell count was 27,000 per cubic millimeter; 85 per cent. of the white cells were polymorphonuclear neutrophils. The examination was otherwise negative.

The patient gave a history of a bilious attack fifteen years before, of an acute arthritis of the right knee three years before and of many attacks of severe pain in the chest, believed to have been of cardiac origin, distributed over a period of three months, two years before. In August, 1919, she was "overcome by the heat." She had another attack of severe pain in the chest at this time. In September, an indolent ulcer appeared on the right great toe and persisted for more than a month.

Operation.—A perinephritic abscess was suspected, and operation was advised. A posterior incision revealed a normal kidney. The peritoneal

cavity was then opened by an anterior incision, and the spleen, which was very large and so completely infarcted that practically no normal splenic tissue remained, was removed. The patient developed a right-sided pneumothorax following the operation; otherwise the postoperative period was uneventful.

Course.—The nutrition and the general clinical condition improved gradually until March, 1920, when the patient began to be troubled by ascites. The abdomen was tapped three times at intervals of two weeks; on each occasion, about 80 ounces (2,400 c.c.) of a straw colored fluid of low specific gravity was removed. On each of the last two occasions, the left pleural cavity was also punctured and about 40 c.c. of fluid similar to that taken from the peritoneal cavity was obtained. After the third tapping, the patient began to have diarrhea, and this so favorably influenced the water balance that no more fluid accumulated in the serous cavities.

In May, there was an acute left axillary adenitis, associated with edema of the arm, which cleared up spontaneously after about one week. The patient had several attacks of acute gastro-enteritis. The Wassermann reaction and the complement fixation test for tuberculosis were both negative (August 3). Several blod examinations were made, all revealing a marked leukocytosis.

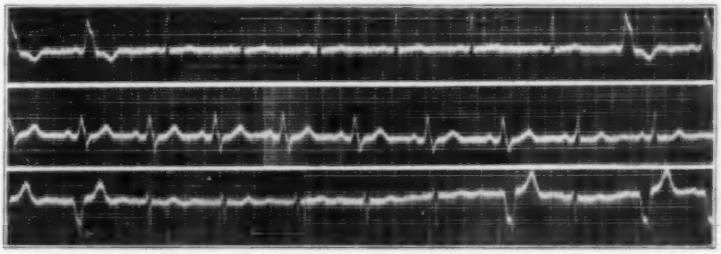

Fig. 6 (Case 3).—Sudden transitions from bundle branch block complexes to complexes suggestive of left ventricular preponderance, and vice versa. These transitions were brought about by forced respiration. Several complexes which followed Cycle 5 (Lead III) were removed in order to shorten the bottom strip of record.

In February, 1921, the patient was greatly improved. She had been carrying on a large amount of administrative work and had no symptoms other than constipation, intense pruritis over the entire body, and slight edema of the ankles in the evening.

Further Findings.—The temperature and the blood pressure were normal, and the lungs and pleurae clear. A soft systolic murmur was heard in the mitral area. There was no ascites. The liver edge was palpable 6 or 8 cm. below the costal margin. The urine contained a trace of albumin and a few granular casts. The blood still showed a severe leukocytosis.

Two sets of electrocardiograms were made at this time. The first curves were characteristic of complete right bundle branch block. It was noted that, when the patient was asked to breathe deeply, a sudden change in the form of the electrocardiogram took place. Figure 6 shows that the bundle branch block complexes suddenly gave place to complexes suggestive of left ventricular preponderance. After a period of from a few seconds to a few minutes, the bundle branch block complexes invariably returned. All of the transitions took place suddenly.

At the time of the second examination, the patient was brought to the laboratory in a wheel chair (she had walked on the first occasion); and the

bundle branch block complexes were not present. They appeared, however, for a short time following mild exercise which consisted in from six to eight forward and sideward movements of the arms with a 5-pound dumbbell in each hand. As on the first occasion, all transitions from bundle branch block complexes to preponderance complexes took place suddenly; no transitional complexes were observed at any time.

Comment.—The sudden onset of bundle branch block is analogous to the sudden onset of complete auriculoventricular block, an instance of which is described in this article. It differs in that it produces no symptoms and cannot be recognized without electrocardiographic records. In this instance, there was a relation between the appearance and the disappearance of the block and the variations in vagal tone produced by forced respiration and by exertion. In this respect, the case is similar to one reported by Wilson.[4] In that instance, however, complexes of transitional form occurred, and the onset of bundle branch block was accompanied by a shift in the location of the pacemaker.

IV

STOKES-ADAMS ATTACKS DUE TO THE SUDDEN ONSET OF COMPLETE BLOCK

CASE 4.—*History.*—Mr. T. H., an American coal miner, aged 39, was admitted to the University Hospital, April 4, 1922, complaining of pain in the right upper quadrant of the abdomen, shortness of breath and palpitation.

The patient gave a history of "inflammatory rheumatism" at the age of 18, in which the muscles of the legs were involved, but the joints were not red or swollen. He was ill for four or five weeks. No history of venereal disease was given, and the Wassermann test was negative.

The illness which brought the patient to the hospital began in September, 1921, with pain in the right upper quadrant of the abdomen. The pain was usually dull, but from time to time sharp stabbing pains were felt. The pain was not related to the taking of food and alkalis did not relieve it. It gradually grew worse, until in December he was forced to quit work. After five weeks in bed, he felt better, but when he tried to work the pain returned. He had never vomited. The pain was never precordial or substernal and it never radiated into the left arm. He had noticed some palpitation and shortness of breath since the onset of his illness.

Examination.—Except for the cardiac abnormalities noted below, the physical examination was entirely negative. The apex beat was in the fifth interspace, 12.5 cm. from the midline. There was no increased dulness to the right of the sternum. There was a conspicuous systolic thrill at the aortic cartilage and in the suprasternal notch. Auscultation disclosed a rough aortic systolic murmur and a blowing aortic diastolic murmur. A mitral systolic murmur was also heard. The pulse showed no abnormalities; the radial artery was moderately sclerosed. The systolic blood pressure was 115, the diastolic, 105. Orthodiagraphic examination revealed a transversely placed, enlarged ventricular shadow; the aorta appeared to be lengthened and tortuous. The right border of the heart shadow measured 50 mm., the left border, 105 mm., from the midline. A roentgen-ray examination of the gastro-intestinal tract showed a twenty-four hour appendiceal shadow and abnormal irritability of the duodenal cap.

Diagnosis.—The roentgenologist made a tentative diagnosis of duodenal ulcer or chronic appendicitis, but his findings were too vague to be conclusive. There was a slight secondary anemia. The urine was normal.

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4. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**:1008, 1915.

The provisional diagnosis was rheumatic heart disease with aortic insufficiency, and possibly aortic stenosis and slight cardiac weakness. The pain was believed to be the result of some intra-abdominal condition, probably duodenal ulcer; but the possibility that it was a cardiac pain of unusual distribution could not be ruled out.

Clinical Course.—Shortly after the patient entered the hospital, he began to have attacks of Stokes-Adams syndrome of varying severity. In the milder attacks, the pulse disappeared for four or five seconds, the respirations deepened, the face became intensely flushed and consciousness was momentarily lost. In the longer attacks, the cyanosis and dyspnea were more conspicuous, and convulsions of a clonic type occurred. The patient often had fifteen or more attacks in as many minutes, and he had as many as thirty-four attacks in one day. Between April 6 and June 24, he had one or more attacks on thirty-six days and was free of attacks on forty-four days. He was often free of attacks for several days in succession (April 6-13, April 17-24, and May 15-29), and then had attacks daily for a similar period (April 25-29, April 30-May 5, June 6-12).

In view of the great irregularity with which the attacks occurred ,it was difficult to determine the effect of various procedures on them. Epinephrin chlorid in doses of 15 minims of a 1:1,000 solution intramuscularly appeared to relieve the patient on a few occasions. May 4, he had several minor attacks at 3 p. m.; epinephrin was given immediately, and at 3:30 p. m., the pulse rate was 68 per minute and the rhythm was regular. At 6 p. m., there was a recurrence of attacks; the heart rate was 36 per minute, and the pulse was weak and irregular. Epinephrin was given at once; at 6:05, the pulse rate was 40; at 6:10, 48; at 6:15, 60, and at 6:30, 72. It is questionable whether the change in pulse rate should be ascribed to the drug, since similar changes in pulse rate occurred with a disappearance of the attacks on other occasions, when no epinephrin was given. On several occasions, atropin sulphate in doses of one-fiftieth grain was given hypodermically, but it produced no obvious effect. From May 18 until June 24, barium chlorid in doses of one-half grain was given, three times daily by mouth. This drug was given on the advice of Dr. S. A. Levine, who pointed out to the authors that certain experimental work on barium indicated that it might enhance the idioventricular rate and possibly prevent ventricular standstill. In this instance, it had no effect on the frequency of the attacks.

During the patient's stay in the hospital, he had several attacks of severe abdominal pain, requiring morphin, and he suffered at intervals from less severe distress in the epigastrium that seemed to be relieved by antacids and an ulcer diet. The patient left the hospital, June 24, somewhat improved; but a follow-up report states that he died suddenly while at table, September 8.

When the patient entered the hospital, no facilities for taking graphic records were available. Early in June, an electrocardiographic outfit was installed, and records were made on several occasions. On two of these occasions, the patient was having attacks.

Electrocardiographic Records.—The records made when the patient was free of attacks show a normal auriculoventricular sequence, with a slight prolongation of the P-R interval which measures 0.22 second (Fig. 7). The ventricular complexes are abnormal in form and show a decided prolongation of the Q-R-S interval, which measures 0.13 second.

June 10, a record was made while the patient was having severe attacks. It shows the end of one period of ventricular standstill and major part of another (Fig. 8). This record is tabulated below. Only R-R intervals are given except during the periods of ventricular standstill, when P-P intervals are given. In this as in those tabulations which follow, the letter R indicates that the corresponding ventricular complex occurs in response to an auricular stimulus; idioventricular beats which gave complexes of the

supraventricular type are represented by the letters Ivc; complexes of ventricular origin but of abnormal form are represented by the letters Abc. When the origin of a ventricular complex is uncertain, the corresponding symbol is followed by a question mark. The intervals given are correct within 0.04 second.

Record Made June 10: P, 0.60; P, 0.56; P, 0.52; P, 0.56; P, 0.52; P, 0.50; P, 0.52; P, 0.52; P, 0.26; Abc, 0.24; P, 0.52; P, 0.16; R, 0.48; R, 0.49; R, 0.49; R, 0.49; R, 0.49; R, 0.49; R, 0.50; R, 0.52; R, 0.58; R, 0.64; R, 0.66; R, 0.78; R, 0.97; R, 1.04; P, 1.04; P, 0.92; P, 0.60; P, 0.60; R, 0.56; P, 0.52; P, 0.52; P, 0.52; P, 0.52; P, 0.52; P, 0.52; P, 0.50; P, 0.52; P, 0.48; P, 0.52; P, 0.52; P, 0.48; P, 0.52; P, 0.48; P, 0.50; P, 0.48; P, 0.48; P, 0.48; P, 0.48; P, 0.48; P, 0.48; P, 0.48; P, convulsion.

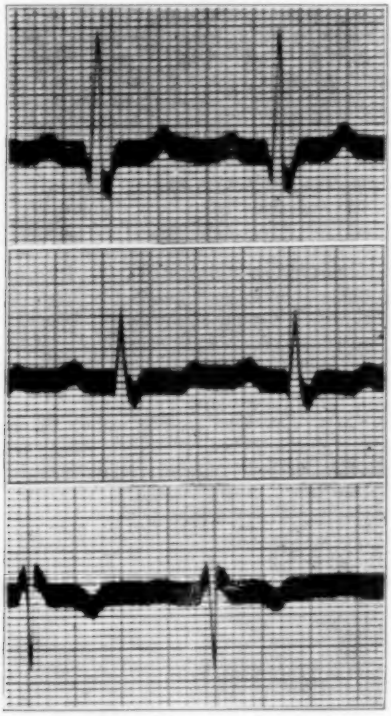

Fig. 7 (Case 4).—Electrocardiogram taken when the patient was free of Stokes-Adams attacks.

The record begins with nine isolated auricular complexes followed by an abnormal ventricular complex, indicating the formation of an impulse in one of the lower ventricular centers. The normal mechanism is then resumed, but after sixteen cycles of normal auriculoventricular sequence, another period of ventricular standstill occurs. After seventeen seconds of ventricular inactivity, the patient had a convulsion and withdrew his hands from the immersion electrodes. The period of ventricular standstill is preceded by conspicuous slowing of the auricular rate, but there is no change in the P-R interval.

During the period of ventricular standstill, the auricular rate rapidly rises; this is usual,[5] and is probably the result of a decrease in vagal tone dependent on the fall in blood pressure.

There can be no doubt that the ventricular standstill was brought about by the abrupt onset of complete heart block. As is well known the ventricular centers require a certain length of time to develop a rhythm, and consequently a period of ventricular standstill invariably results when the functional connection between auricles and ventricles is suddenly interrupted.

June 23, other periods of ventricular standstill were recorded; the attacks at this time were of a milder type. The records obtained are tabulated below. Only R-R intervals are given.

Records Obtained June 23: 6.20, Ivc, 1.04; R, 0.48; R, 0.52; R, 0.48; R, 0.52; R, 0.52; R, 0.48; R, 0.52; R, 0.72; R, 0.72; R, 0.96; R, 0.88; R, 0.84; R, 0.96; R, 0.72; R? 1.56; Abc, 0.60; R? 1.64; Abc, 0.80; R, 0.64; R, 1.64; Abc, 0.84; R, 0.56; R, 0.64; R, 1.72; Abc, 1.16; R, 0.76; R, 0.84; R, 0.84; R, 0.92; R, and twenty-one other normal ventricular complexes.

2.32, Ivc, 0.96; R, 0.52; R, 0.52; R, 0.52; R, 0.56; R, 0.64; R, 0.80; R, 0.88; R, 1.80; Abc, 4.68; R? 0.60; R. 0.56; R, 0.60; R. 0.92; R, 0.76; R, 4.64; Ivc, 1.04; R, 0.52; R? 0.84; R, 0.80.

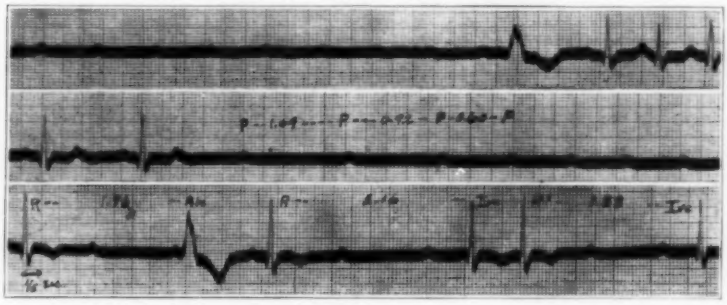

Fig. 8 (Case 4).—Lead I: top record: The end of a period of ventricular standstill; middle record: the beginning of a long period of ventricular standstill (taken, June 10, 1922); bottom record: a period of very mild attacks (taken June 23).

R, 0.68; R, 0.72; R, 3.12; Abc, 1.68; Abc, 2.44; Ivc, 0.80; R, 0.64; R, 0.76; R, 3.20; Abc, 0.68; R, 0.68; R, 0.68; R, 0.84; R, 0.92; R, 2.40; Ivc, 2.20; Ivc, 2.16; Ivc, 0.92; R, 0.60; R, 0.72; R, 0.76; R, 2.32; Ivc, 2.16; Ivc, 0.52; R? 0.72; R, 0.68; R, 0.76; R, 0.88; R, 0.88; R, 2.32; Ivc, 2.16; Ivc, 2.08; Ivc, 0.96; R, 0.60; R, 0.72; R, 0.80; R, 1.76; Abc, 0.96; R, 2.16; Ivc, 0.56; R? 1.88; Ivc, 2.12; Ivc, 0.52; R? 0.68; R, 0.68; R, 0.76; R, 2.20; Ivc, 2.12; Ivc, 0.52; R? 0.70; R, 0.68; R, 0.84; R, 2.20; Ivc, 2.08; Ivc, 0.88; R, 0.72; R, 0.84.

R, 0.72; R, 0.76; R, 0.80; R, 2.12; Ivc, 0.60; R (aberrant), 1.92; Ivc, 0.60; R, 0.80; R, 0.76.

R, 0.80; R, 0.88; R, 2.04; Ivc, 0.84; R, 2.00; Ivc, 0.88; R, 1.96; Ivc, 2.00; Ivc, 0.76; R, 0.68; R, 0.72; R, 0.84; R, 2.08; Ivc, 1.80; Abc, 1.12; R, 0.64; R, 0.72.

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Comment.—The mild nature of the attacks at this time was due, first, to the irregular formation of impulses by one of the lower ventricular centers, and later to the development of an idioventricular rhythm, a center situated above the bifurcation of the His bundle acting as pacemaker. All of the longer periods of ventricular standstill occurred at the beginning of the period of observation. The natural period of the Ivc center appears to have been about 2.0 seconds, while that of the Abc center was about 1.6 to 1.8 seconds (Fig. 8). The latter would probably have acted as pace-maker had it been able to produce impulses regularly. The irregular formation of impulses by some of the lower ventricular centers appears to be a common phenomenon when periods of ventricular standstill occur in rapid succession. It is possible that mechanical factors associated with the overdistension of the ventricles or with the auricular contractions may play a part in their initiation. These records suggest that there was a reciprocal relation between the severity of the attacks and their frequency. A number of attacks of ventricular standstill in close succession allowed the idioventricular rhythm to develop.

The cause of the sudden onset of complete block is not clear. A case identical with ours has been reported by Lewis;[6] in a somewhat similar case, Cohn, Holmes and Lewis[7] on histologic examination of the heart, found large blood sinuses in the A-V bundle. It seemed probable that transient engorgement of these sinuses might have led to the sudden attacks of heart block which were observed during life.

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